# The Concise Guide to PHARMACOLOGY 2023/24: Transporters

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**Abstract**

The Concise Guide to PHARMACOLOGY 2023/24 is the sixth in this series of biennial publications. The Concise Guide provides concise overviews, mostly in tabular format, of the key properties of approximately 1800 drug targets, and over 6000 interactions with about 3900 ligands. There is an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (https://www.guidetopharmacology.org/), which provides more detailed views of target and ligand properties. Although the Concise Guide constitutes almost 500 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.16182. Transporters are one of the six major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ion channels, nuclear hormone receptors, catalytic receptors and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2023, and supersedes data presented in the 2021/22, 2019/20, 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

**Conflict of interest**

The authors state that there are no conflicts of interest to disclose.

**Overview**: The majority of biological solutes are charged organic or inorganic molecules. Cellular membranes are hydrophobic and, therefore, effective barriers to separate them allowing the formation of gradients, which can be exploited, for example, in the generation of energy. Membrane transporters carry solutes across cell membranes, which would otherwise be impermeable to them. The energy required for active transport processes is obtained from ATP turnover or by exploiting ion gradients.

ATP-driven transporters can be divided into three major classes: P-type ATPases; F-type or V-type ATPases and ATP-binding cassette transporters. The first of these, P-type ATPases, are multimeric proteins, which transport (primarily) inorganic cations. The second, F-type or V-type ATPases, are proton-coupled motors, which can function either as transporters or as motors. Last, are ATP-binding cassette transporters, heavily involved in drug disposition as well as transporting endogenous solutes.

The second largest family of membrane proteins in the human genome, after the G protein-coupled receptors, are the SLC solute carrier family. Within the solute carrier family, there are a great variety of solutes transported, from simple inorganic ions to amino acids and sugars to relatively complex organic molecules like haem. The solute carrier family includes 65 families of almost 400 members. Many of these overlap in terms of the solutes that they carry. For example, amino acids accumulation is mediated by members of the SLC1, SLC3/7, SLC6, SLC15, SLC16, SLC17, SLC32, SLC36, SLC38 and SLC43 families. Further members of the SLC superfamily regulate ion fluxes at the plasma membrane, or solute transport into and out of cellular organelles. Some SLC family members remain orphan transporters, in as much as a physiological function has yet to be dtermined. Within the SLC superfamily, there is an abundance in diversity of structure. Two families (SLC3 and SLC7) only generate functional transporters as heteromeric partners, where one partner is a single TM domain protein. Membrane topology predictions for other families suggest 3,4,6,7,8,9,10,11,12,13 or 14 TM domains. The SLC transporters include members which function as antiports, where solute movement in one direction is balanced by a solute moving in the reverse direction. Symports allow concentration gradients of one solute to allow co-transport of a second solute across a membrane. A third, relatively small group are equilibrative transporters, which allow solutes to travel across membranes down their concentration gradients. A more complex family of transporters, the SLC27 fatty acid transporters also exhibit enzymatic function. Many of the transporters also manifest electrogenic properties of ion channels.

## Family structure

# ATP-binding cassette transporter family

Transporters → ATP-binding cassette transporter family

**Overview**: ATP-binding cassette transporters are ubiquitous membrane proteins characterized by active ATP-dependent movement of a range of substrates, including ions, lipids, peptides, steroids. Individual subunits are typically made up of two groups of 6TM-spanning domains, with two nucleotide-binding domains (NBD). The majority of eukaryotic ABC transporters are 'full' transporters incorporating both TM and NBD entities. Some ABCs, notably the ABCD and ABCG families are half-transporters with only a single membrane spanning domain and one NBD, and are only functional as homo- or heterodimers. Eukaryotic ABC transporters convey substrates from the cytoplasm, either out of the cell or into intracellular organelles. Their role in the efflux of exogenous compounds, notably chemotherapeutic agents, has led to considerable interest.

# ABCA subfamily

Transporters → ATP-binding cassette transporter family → ABCA subfamily

**Overview**: To date, 12 members of the human ABCA subfamily are identified. They share a high degree of sequence conservation and have been mostly related with lipid trafficking in a wide range of body locations. Mutations in some of these genes have been described to cause severe hereditary diseases related with lipid transport, such as fatal surfactant deficiency or harlequin ichthyosis. In addition, most of them are hypothesized to participate in the subcellular sequestration of drugs, thereby being responsible for the resistance of several carcinoma cell lines against drug treatment [9, 11].

| Nomenclature | ABCA1 | ABCA3 | ABCA4 |
|---|---|---|---|
| Common abbreviation | ABC1, CERP | ABC3, ABCC | ABCR |
| HGNC, UniProt | *ABCA1*, O95477 | *ABCA3*, Q99758 | *ABCA4*, P78363 |
| Selective ligands | bihelical apoA-I mimetic peptide 5A (Binding) [654] | – | – |
| Selective inhibitors | probucol [215, 798] | – | – |
| Comments | – | Loss-of-function mutations are associated with pulmonary surfactant deficiency | Retinal-specific transporter of N-retinylPE; loss-of-function mutations are associated with childhood-onset Stargardt disease, a juvenile onset macular degenerative disease. The earlier onset disease is often associated with the more severe and deleterious *ABCA4* variants [239].<br>ABCA4 facilitates the clearance of all-*trans*-retinal from photoreceptor disc membranes following photoexcitation. ABCA4 can also transport N-11-*cis*-retinylidene-phosphatidylethanolamine, the Schiff-base adduct of 11-*cis*-retinal; loss of function mutation cause a buildup of lipofuscin, atrophy of the central retina, and severe progressive loss in vision [593]. |

| Nomenclature | ABCA5 | ABCA6 | ABCA7 | ABCA12 |
|---|---|---|---|---|
| HGNC, UniProt | *ABCA5*, Q8WWZ7 | *ABCA6*, Q8N139 | *ABCA7*, Q8IZY2 | *ABCA12*, Q86UK0 |
| Comments | ABCA5 is a lysosomal protein whose loss of function compromises integrity of lysosomes and leads to intra-endolysosomal accumulation of cholesterol. It has recently been associated with Congenital Generalized Hypertrichosis Terminalis (CGHT), a hair overgrowth syndrome, in a patient with a mutation in *ABCA5* that significantly decreased its expression [164]. | A recent genome wide association study identified an *ABCA6* variant associated with cholesterol levels [745]. | Genome wide association studies identify *ABCA7* variants as associated with Alzheimer's Disease [339]. | Reported to play a role in skin ceramide formation [861]. A recent study shows that *ABCA12* expression also impacts cholesterol efflux from macrophages. ABCA12 is postulated to associate with ABCA1 and LXR beta, and stabilize expression of *ABCA1*. ABCA12 deficiency causes decreased expression of *Abca1*, *Abcg1* and *Nr1h2* [237]. |

**Comments**: A number of structural analogues are not found in man: Abca14 (ENSMUSG00000062017); Abca15 (ENSMUSG00000054746); Abca16 (ENSMUSG00000051900) and Abca17 (ENSMUSG00000035435).

# ABCB subfamily

Transporters → ATP-binding cassette transporter family → ABCB subfamily

**Overview**: The ABCB subfamily is composed of four full transporters and two half transporters. This is the only human subfamily to have both half and full types of transporters. ABCB1 was discovered as a protein overexpressed in certain drug resistant tumor cells. It is expressed primarily in the blood brain barrier and liver and is thought to be involved in protecting cells from toxins. Cells that overexpress this protein exhibit multi-drug resistance [11, 159].

| Nomenclature | ABCB1 | ABCB2 | ABCB3 | ABCB4 |
|---|---|---|---|---|
| Common abbreviation | MDR1, PGP1 | TAP1 | TAP2 | PGY3 |
| HGNC, UniProt | *ABCB1*, P08183 | *TAP1*, Q03518 | *TAP2*, Q03519 | *ABCB4*, P21439 |
| Comments | Responsible for the cellular export of many therapeutic drugs. The mouse and rat have two Abcb1 genes (gene names; *Abcb1a* and *Abcb1b*) while the human has only the one gene, *ABCB1*. | Endoplasmic reticulum peptide transporter is a hetero-dimer composed of the two half-transporters, TAP1 (ABCB2) and TAP2 (ABCB3). The transporter shuttles peptides into the endoplasmic reticulum where they are loaded onto major histocompatibility complex class I (MHCI) molecules via the macromoldecular peptide-loading complex and are eventually presented at the cell surface, attributing to TAP an important role in the adaptive immune response [655]. | Endoplasmic reticulum peptide transporter is a hetero-dimer composed of the two half-transporters, TAP1 (ABCB2) and TAP2 (ABCB3). The transporter shuttles peptides into the endoplasmic reticulum where they are loaded onto major histocompatibility complex class I (MHCI) molecules *via* the macromolecular peptide-loading complex and are eventually presented at the cell surface, attributing to TAP an important role in the adaptive immune response [655]. | Transports phosphatidylcholine from intracellular to extracellular face of the hepatocyte canalicular membrane [563]. Heterozygous *ABCB4* variants contribute to mild cholestatic phenotypes, while homozygous deficiency leads to Progressive Intrahepatic Familial Cholestasis (PFIC) Type 3, and increased risk of cholesterol gallstones [335]. |

| Nomenclature | ABCB5 | ABCB6 | ABCB7 |
|---|---|---|---|
| Common abbreviation | – | MTABC3 | ABC7 |
| HGNC, UniProt | *ABCB5*, Q2M3G0 | *ABCB6*, Q9NP58 | *ABCB7*, O75027 |
| Comments | A drug efflux transporter that has been shown to identify cancer stem-like cells in diverse human malignancies, and is also identified as a limbal stem cell that is required for corneal development and repair [429, 790]. | Putative mitochondrial porphyrin transporter [426]; other subcellular localizations are possible, such as the plasma membrane, as a specific determinant of the Langereis blood group system [328]. Loss of *Abcb6* expression in mice leads to decreased expression and activity of CYP450 [116]. | Mitochondrial; reportedly essential for haematopoiesis [583]. Deletion studies in mice demonstrate that *Abcb7* is essential in mammals and substantiate a role for mitochondria in cytosolic Fe-S cluster assembly [582]. |

| Nomenclature | ABCB8 | ABCB9 | ABCB10 | ABCB11 |
|---|---|---|---|---|
| Common abbreviation | MABC1 | TAPL | MTABC2 | ABC16 |
| HGNC, UniProt | *ABCB8*, Q9NUT2 | *ABCB9*, Q9NP78 | *ABCB10*, Q9NRK6 | *ABCB11*, O95342 |
| Ligands | – | – | – | glycochenodeoxycholic acid (Binding) ($pK_i$ 5.2) [102] |

| | | | | |
|---|---|---|---|---|
| Comments | Mitochondrial; suggested to play a role in chemoresistance of melanoma [196]. Cardiac specific deletion of *Abcb8* leads to cardiomyopathy and accumulation of mitochondrial iron, and is thus thought to modulate mitochondrial iron export [350]. | A homodimeric transport complex that translocates cytosolic peptides into the lumne of lysosome for degradation [162]. | Mitochondrial location; the first human ABC transporter to have a crystal structure reported [663]. ABCB10 is important in early steps of heme synthesis in the heart and is required for normal red blood cell development [53, 702]. | Loss-of-function mutations are associated with progressive familial intrahepatic cholestasis type 2 [680]. ATP-dependent transport of bile acids into the confines of the canalicular space by ABCB11 (BSEP) generates an osmotic gradient and thereby, bile flow. Mutations in BSEP that decrease its function or expression cause Progressive Familial Cholestasis Type 2 (PFIC2), which in severe cases, can be fatal in the absence of a liver transplant. Drugs that inhibit BSEP function with IC50 values less than 25 $\mu$M [522] or decrease its expression [253] can cause Drug-Induced Liver Injury (DILI) in the form of cholestatic liver injury. |

# ABCC subfamily

Transporters → ATP-binding cassette transporter family → ABCC subfamily

**Overview**: Subfamily ABCC contains thirteen members and nine of these transporters are referred to as the Multidrug Resistance Proteins (MRPs). The MRP proteins are found throughout nature and they mediate many important functions. They are known to be involved in ion transport, toxin secretion, and signal transduction [11, 159].

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | ABCC1 | ABCC2 | ABCC3 | ABCC4 | ABCC5 |
| Common abbreviation | MRP1 | MRP2, cMOAT | MRP3 | MRP4 | MRP5 |
| HGNC, UniProt | *ABCC1*, P33527 | *ABCC2*, Q92887 | *ABCC3*, O15438 | *ABCC4*, O15439 | *ABCC5*, O15440 |
| Inhibitors | WP814 ($pK_i$ 7.2) [588] | PAK-104P ($pK_i$ 5.4) [124] | – | estradiol disulfate ($pIC_{50}$ 6.7) [835] | compound 2 ($pK_i$ 7.2) [627], sildenafil ($pK_i$ 5.9) [627] |
| Comments | Exhibits a broad substrate specificity [44], including $LTC_4$ ($K_m$ 97 nM [451]) and estradiol-17$\beta$-glucuronide [687]. | Loss-of-function mutations are associated with Dubin-Johnson syndrome, in which plasma levels of conjugated bilirubin are elevated (OMIM: 237500). | Transports conjugates of glutathione, sulfate or glucuronide [79] | Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned [79]; reported to export prostaglandins in a manner sensitive to some cyclooxygenase inhibitors [604] | Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned [79] |

| | | | | |
|---|---|---|---|---|
| Nomenclature | ABCC6 | ATP-binding cassette, sub-family C (CFTR/MRP), member 8 | ABCC9 | ABCC11 |
| Systematic nomenclature | – | ABCC8 | – | – |
| Common abbreviation | MRP6 | SUR1 | SUR2 | MRP8 |
| HGNC, UniProt | *ABCC6*, O95255 | *ABCC8*, Q09428 | *ABCC9*, O60706 | *ABCC11*, Q96J66 |
| Selective inhibitors | – | repaglinide ($pIC_{50}$ 7) [780] | – | – |

| | | | | |
|---|---|---|---|---|
| Comments | Loss-of-function mutations in ABCC6 are associated with pseudoxanthoma elasticum (OMIM: 264800). | The sulfonylurea drugs (acetohexamide, tolbutamide and glibenclamide) act through'sulfonylurea receptors'; tritiated glibenclamide can be used to identify a 140 kDa protein called SUR1 (now known as ABCC8) [603]. | Associated with familial atrial fibrillation, Cantu syndrome and familial isolated dilated cardiomyopathy. | Single nucleotide polymorphisms distinguish wet vs. dry earwax (OMIM: 117800); an association between earwax allele and breast cancer risk is reported in Japanese but not European populations. |

**Comments**: ABCC7 (also known as CFTR, a 12TM ABC transporter-type protein, is a cAMP-regulated epithelial cell membrane $Cl^-$ channel involved in normal fluid transport across various epithelia and can be viewed in the Chloride channels section of the Guide. ABCC8 (ENSG00000006071, also known as SUR1, sulfonylurea receptor 1) and ABCC9 (ENSG00000069431, also known as SUR2, sulfonylurea receptor 2) are unusual in that they lack transport capacity but regulate the activity of particular $K^+$ channels (Kir6.1-6.2), conferring nucleotide sensitivity to these channels to generate the canonical $K_{ATP}$ channels. ABCC13 (ENSG00000155288) is a possible pseudogene.

# ABCD subfamily of peroxisomal ABC transporters

Transporters → ATP-binding cassette transporter family → ABCD subfamily of peroxisomal ABC transporters

**Overview**: Peroxisomes are indispensable organelles in higher eukaryotes. They are essential for the oxidation of a wide variety of metabolites, which include: saturated, monounsaturated and polyunsaturated fatty acids, branched-chain fatty acids, bile acids and dicarboxylic acids [397]. However, the peroxisomal membrane forms an impermeable barrier to these metabolites. The mammalian peroxisomal membrane harbours three ATP-binding cassette (ABC) half-transporters, named ABCD1, -2 and -3. The ABCD transporters predominantly act as homodimers to transport different acyl-CoAs.

| | | | |
|---|---|---|---|
| Nomenclature | ABCD1 | ABCD2 | ABCD3 |
| Common abbreviation | ALDP | ALDR | PMP70 |
| HGNC, UniProt | *ABCD1*, P33897 | *ABCD2*, Q9UBJ2 | *ABCD3*, P28288 |
| Comments | Transports coenzyme A esters (CoA) of very long chain fatty acids (VLCFA) [746, 747]. Pathogenic variants in *ABCD1* (https://adrenoleukodystrophy.info/) result in adrenoleukodystrophy (OMIM: 300100) [396, 489]. | *In vitro* experiments indicate that ABCD2 has overlapping substrate specificity with ABCD1 towards saturated and monounsaturated very long-chain fatty acids, albeit at much lower specificity. ABCD2 has affinity for the polyunsaturated fatty acids C22:6-CoA and C24:6-CoA. However, *in vivo* evidence for its true function is still lacking. No disease has yet been linked to a deficiency of ABCD2. | Transports long-chain dicarboxylic acids, branched-chain fatty acids and C27 bile acids DHC-CoA and THC-CoA [219]. In mitochondrial fatty acid deficient cells and mice, ABCD3 accepts medium and long-chain fatty acids |

**Comments**: ABCD4 (ENSG00000119688, also known as PMP69, PXMP1-L or P70R) is located at the lysosome and is involved in the transport of vitamin B12 (cobalamin) from lysosomes into the cytosol [137].

# ABCG subfamily

Transporters → ATP-binding cassette transporter family → ABCG subfamily

**Overview**: This family of'half-transporters' act as homo- or heterodimers; particularly ABCG5 and ABCG8 are thought to be obligate heterodimers. The ABCG5/ABCG heterodimer sterol transporter structure has been determined [445], suggesting an extensive intracellular nucleotide binding domain linked to the transmembrane domains by a fold in the primary sequence. The functional ABCG2 transporter appears to be a homodimer with structural similarities to the ABCG5/ABCG8 heterodimer [11, 710].

| Nomenclature | ABCG1 | ABCG2 | ABCG4 | ABCG5 | ABCG8 |
|---|---|---|---|---|---|
| Common abbreviation | ABC8 | ABCP | – | – | – |
| HGNC, UniProt | *ABCG1*, P45844 | *ABCG2*, Q9UNQ0 | *ABCG4*, Q9H172 | *ABCG5*, Q9H222 | *ABCG8*, Q9H221 |
| Inhibitors | – | cyclosporin A ($pK_i$ 6.3) [565] | – | – | – |
| Comments | Transports sterols and choline phospholipids [400] | Exhibits a broad substrate specificity, including urate and haem, as well as multiple synthetic compounds [400]. | Putative functional dependence on ABCG1 | The ABCG5/ABCG8 heterodimer transports phytosterols and cholesterol [445]. Loss-of-function mutations in ABCG5 or ABCG8 are associated with sitosterolemia (OMIM: 210250). | The ABCG5/ABCG8 heterodimer transports phytosterols and cholesterol [445]. Loss-of-function mutations in ABCG5 or ABCG8 are associated with sitosterolemia (OMIM: 210250). |

**Comments on ATP-binding cassette transporter family**: A further group of ABC transporter-like proteins have been identified to lack membrane spanning regions and are not believed to be functional transporters, but appear to have a role in protein translation [123, 569]: ABCE1 (P61221, also known as OABP or 2′-5′ oligoadenylate-binding protein); ABCF1 (Q8NE71, also known as ABC50 or TNF-α-stimulated ABC protein); ABCF2 (Q9UG63, also known as iron-inhibited ABC transporter 2) and ABCF3 (Q9NUQ8).

### Further reading on ATP-binding cassette transporter family


Baker A *et al.* (2015) Peroxisomal ABC transporters: functions and mechanism. *Biochem Soc Trans* **43**: 959-65 [PMID:26517910]

Beis K. (2015) Structural basis for the mechanism of ABC transporters. *Biochem Soc Trans* **43**: 889-93 [PMID:26517899]

Chen Z *et al.* (2016) Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade. *Cancer Lett* **370**: 153-64 [PMID:26499806]

Kemp S *et al.* (2011) Mammalian peroxisomal ABC transporters: from endogenous substrates to pathology and clinical significance. *Br J Pharmacol* **164**: 1753-66 [PMID:21488864]

Kerr ID *et al.* (2011) The ABCG family of membrane-associated transporters: you don't have to be big to be mighty. *Br J Pharmacol* **164**: 1767-79 [PMID:21175590]

Kloudova A *et al.* (2017) The Role of Oxysterols in Human Cancer. *Trends Endocrinol Metab* **28**: 485-496 [PMID:28410994]

López-Marqués RL *et al.* (2015) Structure and mechanism of ATP-dependent phospholipid transporters. *Biochim Biophys Acta* **1850**: 461-475 [PMID:24746984]

Neul C *et al.* (2016) Impact of Membrane Drug Transporters on Resistance to Small-Molecule Tyrosine Kinase Inhibitors. *Trends Pharmacol Sci* **37**: 904-932 [PMID:27659854]

Peña-Solórzano D *et al.* (2017) ABCG2/BCRP: Specific and Nonspecific Modulators. *Med Res Rev* **37**: 987-1050 [PMID:28005280]

Vauthier V *et al.* (2017) Targeted pharmacotherapies for defective ABC transporters. *Biochem Pharmacol* **136**: 1-11 [PMID:28245962]

# F-type and V-type ATPases

Transporters → F-type and V-type ATPases

**Overview**: The F-type (ATP synthase) and the V-type (vacuolar or vesicular proton pump) ATPases, although having distinct subcellular locations and roles, exhibit marked similarities in subunit structure and mechanism. They are both composed of a 'soluble' complex (termed $F_1$ or $V_1$) and a membrane complex ($F_o$ or $V_o$). Within each ATPase complex, the two individual sectors appear to function as connected opposing rotary motors, coupling catalysis of ATP synthesis or hydrolysis to proton transport. Both the F-type and V-type ATPases have been assigned enzyme commission number E.C. 3.6.3.14

# F-type ATPase

Transporters → F-type and V-type ATPases → F-type ATPase

**Overview**: The F-type ATPase, also known as ATP synthase or ATP phosphohydrolase ($H^+$-transporting), is a mitochondrial membrane-associated multimeric complex consisting of two domains, an $F_0$ channel domain in the membrane and an $F_1$ domain extending into the lumen. Proton transport across the inner mitochondrial membrane is used to drive the synthesis of ATP, although it is also possible for the enzyme to function as an ATPase. The ATP5O subunit (oligomycin sensitivity-conferring protein, OSCP, (P48047)), acts as a connector between $F_1$ and $F_0$ motors.

The **$F_1$ motor**, responsible for ATP turnover, has the subunit composition $\alpha 3\beta 3\gamma\delta\epsilon$.

The **$F_0$ motor**, responsible for ion translocation, is complex in mammals, with probably nine subunits centring on A, B, and C subunits in the membrane, together with D, E, F2, F6, G2 and 8 subunits. Multiple pseudogenes for the $F_0$ motor proteins have been defined in the human genome.

Information on members of this family may be found in the online database.

# V-type ATPase

Transporters → F-type and V-type ATPases → V-type ATPase

**Overview**: The V-type ATPase is most prominently associated with lysosomes in mammals, but also appears to be expressed on the plasma membrane and neuronal synaptic vesicles.

The **$V_1$ motor**, responsible for ATP turnover, has eight subunits with a composition of A-H.

The **$V_0$ motor**, responsible for ion translocation, has six subunits (a-e).

Information on members of this family may be found in the online database.

**Further reading on V-type ATPase**

Collins MP *et al.* (2020) Regulation and function of V-ATPases in physiology and disease. *Biochim Biophys Acta Biomembr* **1862**: 183341 [PMID:32422136]

**Further reading on F-type and V-type ATPases**

Brandt K *et al.* (2015) Hybrid rotors in F1F(o) ATP synthases: subunit composition, distribution, and physiological significance. *Biol Chem* **396**: 1031-42 [PMID:25838297]
Krah A. (2015) Linking structural features from mitochondrial and bacterial F-type ATP synthases to their distinct mechanisms of ATPase inhibition. *Prog Biophys Mol Biol* **119**: 94-102 [PMID:26140992]
Marshansky V *et al.* (2014) Eukaryotic V-ATPase: novel structural findings and functional insights. *Biochim Biophys Acta* **1837**: 857-79 [PMID:24508215]
Noji H *et al.* (2017) Catalytic robustness and torque generation of the $F_1$-ATPase. *Biophys Rev* **9**: 103-118 [PMID:28424741]
Okuno D *et al.* (2013) Single-molecule analysis of the rotation of $F_1$-ATPase under high hydrostatic pressure. *Biophys J* **105**: 1635-42 [PMID:24094404]

# P-type ATPases

Transporters → P-type ATPases

**Overview**: Phosphorylation-type ATPases (EC 3.6.3.-) are associated with membranes and the transport of ions or phospholipids. Characteristics of the family are the transient phosphorylation of the transporters at an aspartate residue and the interconversion between E1 and E2 conformations in the activity cycle of the transporters, taken to represent 'half-channels' facing the cytoplasm and extracellular/luminal side of the membrane, respectively.

Sequence analysis across multiple species allows the definition of five subfamilies, P1-P5. The P1 subfamily includes heavy metal pumps, such as the copper ATPases. The P2 subfamily includes calcium, sodium/potassium and proton/potassium pumps. The P4 and P5 subfamilies include putative phospholipid flippases.

# P1B P-type ATPases: $Cu^+$-ATPases

Transporters → P-type ATPases → P1B P-type ATPases: $Cu^+$-ATPases

**Overview**: Copper-transporting ATPases convey copper ions across cell-surface and intracellular membranes. They consist of eight TM domains and associate with multiple copper chaperone proteins (*e.g.* ATOX1, O00244).

Information on members of this family may be found in the online database.

# P2A P-type ATPases: $Ca^{2+}$-ATPases

Transporters → P-type ATPases → P2A P-type ATPases: $Ca^{2+}$-ATPases

**Overview**: The sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA) is an intracellular membrane-associated pump for sequestering calcium from the cytosol into intracellular organelles, usually associated with the recovery phase following excitation of muscle and nerves.

The plasma membrane $Ca^{2+}$-ATPase (PMCA) is a cell-surface pump for extruding calcium from the cytosol, usually associated with the recovery phase following excitation of cells. The active pump is a homodimer, each subunit of which is made up of ten TM segments, with cytosolic C- and N-termini and two large intracellular loops.

Secretory pathway $Ca^{2+}$-ATPases (SPCA) allow accumulation of calcium and manganese in the Golgi apparatus.

Information on members of this family may be found in the online database.

**Comments**: The fungal toxin ochratoxin A has been described to activate SERCA in kidney microsomes [131]. Cyclopiazonic acid [651], thapsigargin [478] and BHQ are widely employed to block SERCA. Thapsigargin has also been described to block the TRPV1 vanilloid receptor [726].

The stoichiometry of flux through the PMCA differs from SERCA, with the PMCA transporting 1 $Ca^{2+}$ while SERCA transports 2 $Ca^{2+}$.

Loss-of-function mutations in SPCA1 appear to underlie Hailey-Hailey disease [344].

# $Na^+/K^+$-ATPases

Transporters → P-type ATPases → P2C P-type ATPases → $Na^+/K^+$-ATPases

**Overview**: The cell-surface $Na^+/K^+$-ATPase is an integral membrane protein which regulates the membrane potential of the cell by maintaining gradients of $Na^+$ and $K^+$ ions across the plasma membrane, also making a small, direct contribution to membrane potential, particularly in cardiac cells. For every molecule of ATP hydrolysed, the $Na^+/K^+$-ATPase extrudes three $Na^+$ ions and imports two $K^+$ ions. The active transporter is a heteromultimer with incompletely defined stoichiometry, possibly as tetramers of heterodimers, each consisting of one of four large, ten TM domain catalytic $\alpha$ subunits and one of three smaller, single TM domain glycoprotein $\beta$-subunits. Additional protein partners known as FXYD proteins (*e.g.* FXYD2, P54710) appear to associate with and regulate the activity of the pump.

Information on members of this family may be found in the online database.

**Comments**: $Na^+/K^+$-ATPases are inhibited by ouabain, and cardiac glycosides such as digoxin, as well as potentially endogenous cardiotonic steroids [41].

# $H^+/K^+$-ATPases

Transporters → P-type ATPases → P2C P-type ATPases → $H^+/K^+$-ATPases

**Overview**: The $H^+/K^+$ ATPase is a heterodimeric protein, made up of $\alpha$ and $\beta$ subunits. The $\alpha$ subunit has 10 TM domains and exhibits catalytic and pore functions, while the $\beta$ subunit has a single TM domain, which appears to be required for intracellular trafficking and stabilising the $\alpha$ subunit. The ATP4A and ATP4B subunits are expressed together, while the ATP12A subunit is suggested to be expressed with the $\beta$1 (ATP1B1) subunit of the $Na^+/K^+$-ATPase [576].

Information on members of this family may be found in the online database.

**Comments**: The gastric $H^+/K^+$-ATPase is inhibited by proton pump inhibitors (PPIs, *e.g.* dexlansoprazole and esomeprazole) which are used to treat excessive gastric acid secretion. PPIs have a gradual onset of action. More quickly acting potassium-competitive acid blockers (P-CABs; *e.g.* vonoprazan, revaprazan and tegoprazan) have now entered the clinic. P-CABs are competitive and reversible $H^+/K^+$-ATPase blockers and their effect on acid suppression is stronger and more sustained compared to PPIs.

**Further reading on $H^+/K^+$-ATPases**

Tanaka S *et al.* (2022) Structural Basis for Binding of Potassium-Competitive Acid Blockers to the Gastric Proton Pump. *J Med Chem* [PMID:35604136]

# P4 P-type ATPases: Phospholipid-transporting ATPases

Transporters → P-type ATPases → P4 P-type ATPases: Phospholipid-transporting ATPases

**Overview**: These transporters are thought to translocate the aminophospholipids phosphatidylserine and phosphatidylethanolamine from one side of the phospholipid bilayer to the other to generate asymmetric membranes. They are also proposed to be involved in the generation of vesicles from intracellular and cell-surface membranes.

Information on members of this family may be found in the online database.

**Comments**: Loss-of-function mutations in ATP8B1 are associated with type I familial intrahepatic cholestasis.

# P5 P-type ATPases: $Mn^{2+}$-ATPases

Transporters → P-type ATPases → P5 P-type ATPases: $Mn^{2+}$-ATPases

**Overview**: P5 subfamily P-type ATPases are cation and lipid pumps that transport inorganic cations and other substrates across cell membranes.

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | ATPase 13A1 | ATPase cation transporting 13A2 | ATPase 13A3 | ATPase 13A4 | ATPase 13A5 |
| HGNC, UniProt | *ATP13A1*, Q9HD20 | *ATP13A2*, Q9NQ11 | *ATP13A3*, Q9H7F0 | *ATP13A4*, Q4VNC1 | *ATP13A5*, Q4VNC0 |
| Comments | – | – | Identified as an important component of the mammalian polyamine transport system [319]. | – | – |

### Further reading on P5 P-type ATPases: $Mn^{2+}$-ATPases

Hamouda NN *et al.* (2020) ATP13A3 is a major component of the enigmatic mammalian polyamine transport system. *J Biol Chem* 296, 100182 [PMID:33310703]

### Further reading on P-type ATPases

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Krebs J. (2015) The plethora of PMCA isoforms: Alternative splicing and differential expression. *Biochim Biophys Acta* **1853**: 2018-24 [PMID:25535949]Little R *et al.* (2016) Plasma membrane calcium ATPases (PMCAs) as potential targets for the treatment of essential hypertension. *Pharmacol Ther* **159**: 23-34 [PMID:26820758]
López-Marqués RL *et al.* (2015) Structure and mechanism of ATP-dependent phospholipid transporters. *Biochim Biophys Acta* **1850**: 461-475 [PMID:24746984]

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Padányi R *et al.* (2016) Multifaceted plasma membrane Ca(2+) pumps: From structure to intracellular Ca(2+) handling and cancer. *Biochim Biophys Acta* **1863**: 1351-63 [PMID:26707182]
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Tadini-Buoninsegni F *et al.* (2017) Mechanisms of charge transfer in human copper ATPases ATP7A and ATP7B. *IUBMB Life* **69**: 218-225 [PMID:28164426]

# SLC superfamily of solute carriers

Transporters → SLC superfamily of solute carriers

**Overview**: The SLC superfamily of solute carriers is the second largest family of membrane proteins after G protein-coupled receptors, but with a great deal fewer therapeutic drugs that exploit them. As with the ABC transporters, however, they play a major role in drug disposition and so can be hugely influential in determining the clinical efficacy of particular drugs.
48 families are identified on the basis of sequence similarities, but many of them overlap in terms of the solutes that they carry. For example, amino acid accumulation is mediated by members of the SLC1, SLC3/7, SLC6, SLC15, SLC16, SLC17, SLC32, SLC36, SLC38 and SLC43. Further members of the SLC superfamily regulate ion fluxes at the plasma membrane, or solute transport into and out of cellular organelles.

Within the SLC superfamily, there is an abundance in diversity of structure. Two families (SLC3 and SLC7) only generate functional transporters as heteromeric partners, where one partner is a single TM domain protein. Membrane topology predictions for other families suggest 3, 4 6, 7, 8, 9, 10, 11, 12, 13, or 14 TM domains. Functionally, members may be divided into those dependent on gradients of ions (particularly sodium, chloride or protons), exchange of solutes or simple equilibrative gating. For many members, the stoichiometry of transport is not yet established. Furthermore, one family of transporters also possess enzymatic activity (SLC27), while many members function as ion channels (*e.g.* SLC1A7/EAAT5), which increases the complexity of function of the SLC superfamily.

# SLC1 family of amino acid transporters

Transporters → SLC superfamily of solute carriers → SLC1 family of amino acid transporters

**Overview**: The SLC1 family of sodium dependent transporters includes the plasma membrane located glutamate transporters and the neutral amino acid transporters ASCT1 and ASCT2 [16, 54, 387, 388, 566].

# Glutamate transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC1 family of amino acid transporters → Glutamate transporter subfamily

**Overview**: Glutamate transporters present the unusual structural motif of 8TM segments and 2 re-entrant loops [299]. The crystal structure of a glutamate transporter homologue (GltPh) from *Pyrococcus horikoshii* supports this topology and indicates that the transporter assembles as a trimer, where each monomer is a functional unit capable of substrate permeation [81, 607, 828] reviewed by [375]). This structural data is in agreement with the proposed quaternary structure for EAAT2 [259] and several functional studies that propose the monomer is the functional unit [292, 416, 441, 626]. Recent evidence suggests that EAAT3 and EAAT4 may assemble as heterotrimers [544]. The activity of glutamate transporters located upon both neurones (predominantly EAAT3, 4 and 5) and glia (predominantly EAAT 1 and 2) serves, dependent upon their location, to regulate excitatory neurotransmission, maintain low ambient extracellular concentrations of glutamate (protecting against excitotoxicity) and provide glutamate for metabolism including the glutamate-glutamine cycle. The $Na^+/K^+$-ATPase that maintains the ion gradients that drive transport has been demonstrated to co-assemble with EAAT1 and EAAT2 [616]. Recent evidence supports altered glutamate transport and novel roles in brain for

splice variants of EAAT1 and EAAT2 [256, 442]. Three patients with dicarboxylic aminoaciduria (DA) were recently found to have loss-of-function mutations in EAAT3 [42]. DA is characterized by excessive excretion of the acidic amino acids glutamate and aspartate and EAAT3 is the predominant glutamate/aspartate transporter in the kidney. Enhanced expression of EAAT2 resulting from administration of $\beta$-lactam antibacterials (*e.g.* ceftriaxone) is neuroprotective and occurs through NF-$\kappa$B-mediated EAAT2 promoter activation [250, 447, 620] reviewed by [402]). PPAR$\gamma$ activation (*e.g.* by rosiglitazone) also leads to enhanced expression of EAAT though promoter activation [615]. In addition, several translational activators of EAAT2 have recently been described [140] along with treatments that increase the surface expression of EAAT2 (*e.g.* [440, 860]), or prevent its down-regulation (*e.g.* [281]). A thermodynamically uncoupled $Cl^-$ flux, activated by $Na^+$ and glutamate [294, 387, 482] ($Na^+$ and aspartate in the case of GltPh [625]), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability [725, 759]. Indeed, it has recently been suggested that the primary function of EAAT5 is as a slow anion channel gated by glutamate, rather than a glutamate transporter [243].

| Nomenclature | Excitatory amino acid transporter 1 | Excitatory amino acid transporter 2 | Excitatory amino acid transporter 3 | Excitatory amino acid transporter 4 | Excitatory amino acid transporter 5 |
|---|---|---|---|---|---|
| Systematic nomenclature | SLC1A3 | SLC1A2 | SLC1A1 | SLC1A6 | SLC1A7 |
| Common abbreviation | EAAT1 | EAAT2 | EAAT3 | EAAT4 | EAAT5 |
| HGNC, UniProt | *SLC1A3*, P43003 | *SLC1A2*, P43004 | *SLC1A1*, P43005 | *SLC1A6*, P48664 | *SLC1A7*, O00341 |
| Substrates | L-trans-2,4-pyrolidine dicarboxylate, DL-threo-$\beta$-hydroxyaspartate ($K_i$ $5.8 \times 10^{-5}$M) [659], D-aspartic acid | DL-threo-$\beta$-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate [417], D-aspartic acid | DL-threo-$\beta$-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid | DL-threo-$\beta$-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid | DL-threo-$\beta$-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid |
| Endogenous substrates | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid | L-cysteine [837], L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid | L-glutamic acid, L-aspartic acid |
| Stoichiometry | Probably 3 $Na^+$: 1 $H^+$ : 1 glutamate (in): 1 $K^+$ (out) | 3 $Na^+$: 1 $H^+$ : 1 glutamate (in): 1 $K^+$ (out) [454] | 3 $Na^+$: 1 $H^+$ : 1 glutamate (in): 1 $K^+$ (out) [838] | Probably 3 $Na^+$: 1 $H^+$ : 1 glutamate (in): 1 $K^+$(out) | Probably 3 $Na^+$: 1 $H^+$ : 1 glutamate (in): 1 $K^+$ (out) |
| Inhibitors | UCPH-101 (membrane potential assay) ($pIC_{50}$ 6.9) [371], DL-TBOA ($pK_B$ 5) [659] | WAY-213613 ($pIC_{50}$ 7.1) [187], DL-TBOA ($pK_B$ 6.9) [659], SYM2081 ($pK_B$ 5.5) [749], dihydrokainate ($pK_B$ 5), threo-3-methylglutamate ($pK_B$ 4.7) [749] | NBI-59159 ($pIC_{50}$ 7.1) [185], L-$\beta$-BA ([$^3$H]D-aspartate uptake assay) ($pK_i$ 6.1) [206], DL-TBOA ($pIC_{50}$ 5.1) [661] | DL-TBOA ($pK_i$ 5.4) [658], threo-3-methylglutamate ($pK_i$ 4.3) [195] | DL-TBOA ($pK_i$ 5.5) [658] |
| Selective allosteric modulators | – | (R)-AS-1 (Positive) ($pEC_{50}$ 8) [2] | – | – | – |
| Labelled ligands | [$^3$H]ETB-TBOA (Binding) ($pK_d$ 7.8) [660] – Rat, [$^3$H]D-aspartic acid, [$^3$H]L-aspartic acid, [$^3$H]SYM2081 | [$^3$H]ETB-TBOA (Binding) ($pK_d$ 7.8) [660] – Rat, [$^3$H]D-aspartic acid, [$^3$H]L-aspartic acid, [$^3$H]SYM2081 | [$^3$H]ETB-TBOA (Binding) ($pK_d$ 6.5) [660] – Rat, [$^3$H]D-aspartic acid, [$^3$H]L-aspartic acid | [$^3$H]ETB-TBOA (Binding) ($pK_d$ 7.9) [660] – Rat, [$^3$H]D-aspartic acid, [$^3$H]L-aspartic acid | [$^3$H]ETB-TBOA (Binding) ($pK_d$ 7.6) [660] – Rat, [$^3$H]D-aspartic acid, [$^3$H]L-aspartic acid |

**Comments**: The $K_B$ (or $K_i$) values reported, unless indicated otherwise, are derived from transporter currents mediated by EAATs expressed in voltage-clamped *Xenopus laevis* oocytes [195, 658, 659, 749]. $K_B$ (or $K_i$) values derived in uptake assays are generally higher (*e.g.* [659]). In addition to acting as a poorly transportable inhibitor of EAAT2, (2S,4R)-4-methylglutamate, also known as SYM2081, is a competitive substrate for EAAT1 ($K_M$ = 54$\mu$M; [346, 749]) and additionally is a potent kainate receptor agonist [849] which renders the compound unsuitable for autoradiographic localisation of EAATs [29]. Similarly, at concentrations that inhibit EAAT2, dihydrokainate binds to kainate receptors [659]. WAY-855 and WAY-213613 are both non-substrate inhibitors with a preference for EAAT2 over EAAT3 and EAAT1 [186, 187]. NBI-59159 is a non-substrate inhibitor with modest selectivity for EAAT3 over EAAT1 (>10-fold) and EAAT2 (5-fold) [141, 184]. Analogously, L-$\beta$-*threo*-benzyl-aspartate (L-$\beta$-BA) is a competitive non-substrate inhibitor that preferentially blocks EAAT3 versus EAAT1, or EAAT2 [206]. [$^3$H]SYM2081 demonstrates low affinity binding ($K_D \cong 6.0$ $\mu$M) to EAAT1 and EAAT2 in rat brain homogenates [31] and EAAT1 in murine astrocyte membranes [30], whereas [$^3$H]ETB-TBOA binds with high affinity to all EAATs other than EAAT3 [660]. The novel isoxazole derivative (-)-HIP-A may interact at the same site as TBOA and preferentially inhibit reverse transport of glutamate [139]. Threo-3-methylglutamate induces substrate-like currents at EAAT4, but does not elicit heteroexchange of [$^3$H]-aspartate in synaptosome preparations, inconsistent with the behaviour of a substrate inhibitor [195]. Parawixin 1, a compound isolated from the venom from the spider *Parawixia bistriata* is a selective enhancer of the glutamate uptake through EAAT2 but not through EAAT1 or EAAT3 [229, 230]. In addition to the agents listed in the table, DL-threo-$\beta$-hydroxyaspartate and L-trans-2,4-pyrolidine dicarboxylate act as non-selective competitive substrate inhibitors of all EAATs. $Zn^{2+}$ and arachidonic acid are putative endogenous modulators of EAATs with actions that differ across transporter subtypes (reviewed by [748]).

# Alanine/serine/cysteine transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC1 family of amino acid transporters → Alanine/serine/cysteine transporter subfamily

**Overview**: ASC transporters mediate $Na^+$-dependent exchange of small neutral amino acids such as Ala, Ser, Cys and Thr and their structure is predicted to be similar to that of the glutamate transporters [34, 743]. ASCT1 and ASCT2 also exhibit thermodynamically uncoupled chloride channel activity associated with substrate transport [11, 91, 839]. Whereas EAATs counter-transport $K^+$ (see above) ASCTs do not and their function is independent of the intracellular concentration of $K^+$ [11, 839].

| | | |
|---|---|---|
| Nomenclature | Alanine/serine/cysteine transporter 1 | Alanine/serine/cysteine transporter 2 |
| Systematic nomenclature | SLC1A4 | SLC1A5 |
| Common abbreviation | ASCT1 | ASCT2 |
| HGNC, UniProt | *SLC1A4*, P43007 | *SLC1A5*, Q15758 |
| Endogenous substrates | L-cysteine > L-alanine = L-serine > L-threonine | L-alanine = L-serine = L-cysteine (low Vmax) = L-threonine = L-glutamine = L-asparagine ≫ L-methionine ≅ glycine ≅ L-leucine > L-valine > L-glutamic acid (enhanced at low pH) |
| Stoichiometry | 1 $Na^+$: 1 amino acid (in): 1 $Na^+$: 1 amino acid (out); (homo-, or hetero-exchange; [838]) | 1 $Na^+$: 1 amino acid (in): 1 $Na^+$: 1 amino acid (out); (homo-, or hetero-exchange; [89]) |
| Inhibitors | – | p-nitrophenyl glutamyl anilide ($pK_i$ 4.3) [207] – Rat, benzylcysteine ($pK_i$ 3.1) [293], benzylserine ($pK_i$ 3) [293] |

**Comments**: The substrate specificity of ASCT1 may extend to L-proline and trans-4-hydroxy-proline [580]. At low pH (~5.5) both ASCT1 and ASCT2 are able to exchange acidic amino acids such as L-cysteate and glutamate [700, 743]. In addition to the inhibitors tabulated above, $HgCl_2$, methylmercury and mersalyl, at low micromolar concentrations, non-competitively inhibit ASCT2 by covalent modificiation of cysteine residues [558].

### Further reading on SLC1 family of amino acid transporters


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# SLC2 family of hexose and sugar alcohol transporters

Transporters → SLC superfamily of solute carriers → SLC2 family of hexose and sugar alcohol transporters

**Overview**: The SLC2 family transports D-glucose, D-fructose, inositol (*e.g.* myo-inositol) and related hexoses. Three classes of glucose transporter can be identified, separating GLUT1-4 and 14, GLUT6, 8, 10 and 12; and GLUT5, 7, 9 and 11. Modelling suggests a 12 TM membrane topology, with intracellular termini, with functional transporters acting as homodimers or homotetramers.

# Class I transporters

Transporters → SLC superfamily of solute carriers → SLC2 family of hexose and sugar alcohol transporters → Class I transporters

**Overview**: Class I transporters are able to transport D-glucose, but not D-fructose, in the direction of the concentration gradient and may be inhibited non-selectively by phloretin and cytochalasin B. GLUT1 is the major glucose transporter in brain, placenta and erythrocytes, GLUT2 is found in the pancreas, liver and kidneys, GLUT3 is neuronal and placental, while GLUT4 is the insulin-responsive transporter found in skeletal muscle, heart and adipose tissue. GLUT14 appears to result from gene duplication of GLUT3 and is expressed in the testes [802].

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | Glucose transporter 1 | Glucose transporter 2 | Glucose transporter 3 | Glucose transporter 4 | Glucose transporter 14 |
| Systematic nomenclature | SLC2A1 | SLC2A2 | SLC2A3 | SLC2A4 | SLC2A14 |
| Common abbreviation | GLUT1 | GLUT2 | GLUT3 | GLUT4 | GLUT14 |
| HGNC, UniProt | *SLC2A1*, P11166 | *SLC2A2*, P11168 | *SLC2A3*, P11169 | *SLC2A4*, P14672 | *SLC2A14*, Q8TDB8 |
| Substrates | dehydroascorbic acid [65], D-glucosamine (D-glucose = D-glucosamine) [739], D-glucose (D-glucose = D-glucosamine) [739] | D-glucosamine (D-glucosamine > D-glucose) [739], D-glucose (D-glucosamine > D-glucose) [739] | D-glucose | D-glucosamine (D-glucosamine ≥ D-glucose) [739], D-glucose (D-glucosamine ≥ D-glucose) [739] | – |
| Labelled ligands | [$^3$H]2-deoxyglucose | [$^3$H]2-deoxyglucose | [$^3$H]2-deoxyglucose | [$^3$H]2-deoxyglucose | – |
| Comments | GLUT1 is a class I facilitative sugar transporter. GLUT1 functions to maintain basal glucose import which is required for cellular respiration. | – | – | – | – |

# Class II transporters

Transporters → SLC superfamily of solute carriers → SLC2 family of hexose and sugar alcohol transporters → Class II transporters

**Overview**: Class II transporters transport D-fructose and appear to be insensitive to cytochalasin B. Class II transporters appear to be predominantly intracellularly located.

| | | | |
|---|---|---|---|
| Nomenclature | Glucose transporter 5 | Glucose transporter 7 | Glucose transporter 9 |
| Systematic nomenclature | SLC2A5 | SLC2A7 | SLC2A9 |
| Common abbreviation | GLUT5 | GLUT7 | GLUT9 |
| HGNC, UniProt | *SLC2A5*, P22732 | *SLC2A7*, Q6PXP3 | *SLC2A9*, Q9NRM0 |
| Substrates | D-fructose (D-fructose > D-glucose) [96], D-glucose (D-fructose > D-glucose) [96] | D-glucose [117], D-fructose [117] | D-fructose [107], uric acid [107] |

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | Glucose transporter 11 | Glucose transporter 6 | Glucose transporter 8 | Glucose transporter 10 | Glucose transporter 12 |
| Systematic nomenclature | SLC2A11 | SLC2A6 | SLC2A8 | SLC2A10 | SLC2A12 |
| Common abbreviation | GLUT11 | GLUT6 | GLUT8 | GLUT10 | GLUT12 |
| HGNC, UniProt | *SLC2A11*, Q9BYW1 | *SLC2A6*, Q9UGQ3 | *SLC2A8*, Q9NY64 | *SLC2A10*, O95528 | *SLC2A12*, Q8TD20 |
| Substrates | D-glucose [174], D-fructose [492] | – | D-glucose [348] | D-glucose [449], dehydroascorbic acid [449] | D-glucose [611] |

# Proton-coupled inositol transporter

Transporters → SLC superfamily of solute carriers → SLC2 family of hexose and sugar alcohol transporters → Proton-coupled inositol transporter

**Overview**: Proton-coupled inositol transporters are expressed predominantly in the brain and can be inhibited by phloretin and cytochalasin B [739].

| | |
|---|---|
| Nomenclature | Proton *myo*-inositol cotransporter |
| Systematic nomenclature | SLC2A13 |
| Common abbreviation | HMIT |
| HGNC, UniProt | *SLC2A13*, Q96QE2 |
| Substrates | *myo*-inositol [739], D-*chiro*-inositol [739], *muco*-inositol [739], *scyllo*-inositol [739] |
| Stoichiometry | 1 $H^+$ : 1 inositol (in) [167] |

**Further reading on SLC2 family of hexose and sugar alcohol transporters**

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Leney SE *et al*. (2009) The molecular basis of insulin-stimulated glucose uptake: signalling, trafficking and potential drug targets. *J Endocrinol* **203**: 1-18 [PMID:19389739]
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# SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)

Transporters → SLC superfamily of solute carriers → SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)

**Overview**: The SLC3 and SLC7 families combine to generate functional transporters, where the subunit composition is a disulphide-linked combination of a heavy chain (SLC3 family) with a light chain (SLC7 family) [11].

# SLC3 family

Transporters → SLC superfamily of solute carriers → SLC3 and SLC7 families of heteromeric amino acid transporters (HATs) → SLC3 family

**Overview**: SLC3 family members are single TM proteins with extensive glycosylation of the exterior C-terminus, which heterodimerize with SLC7 family members in the endoplasmic reticulum and assist in the plasma membrane localization of the transporter.

Information on members of this family may be found in the online database.

# SLC7 family

Transporters → SLC superfamily of solute carriers → SLC3 and SLC7 families of heteromeric amino acid transporters (HATs) → SLC7 family

**Overview**: SLC7 family members may be divided into two major groups: cationic amino acid transporters (CATs) and glycoprotein-associated amino acid transporters (gpaATs).

Cationic amino acid transporters are 14 TM proteins, which mediate pH- and sodium-independent transport of cationic amino acids (system $y^+$), apparently as an exchange mechanism. These transporters are sensitive to inhibition by N-ethylmaleimide.

| Nomenclature | High affinity cationic amino acid transporter 1 | Low affinity cationic amino acid transporter 2 | Cationic amino acid transporter 3 | L-type amino acid transporter 1 | L-type amino acid transporter 2 |
|---|---|---|---|---|---|
| Systematic nomenclature | SLC7A1 | SLC7A2 | SLC7A3 | SLC7A5 | SLC7A8 |
| Common abbreviation | CAT1 | CAT2 | CAT3 | LAT1 | LAT2 |
| HGNC, UniProt | *SLC7A1*, P30825 | *SLC7A2*, P52569 | *SLC7A3*, Q8WY07 | *SLC7A5*, Q01650 | *SLC7A8*, Q9UHI5 |
| Substrates | L-arginine, L-lysine, L-ornithine, L-histidine | L-arginine, L-lysine, L-ornithine, L-histidine | L-arginine, L-lysine, L-ornithine | – | – |
| Selective inhibitors | – | – | – | KYT-0353 [552] | – |

| Nomenclature | y+L amino acid transporter 1 | y+L amino acid transporter 2 | $b^{0,+}$-type amino acid transporter 1 | Asc-type amino acid transporter 1 | Cystine/glutamate transporter | AGT1 |
|---|---|---|---|---|---|---|
| Systematic nomenclature | SLC7A7 | SLC7A6 | SLC7A9 | SLC7A10 | SLC7A11 | SLC7A13 |
| Common abbreviation | y+LAT1 | y+LAT2 | $b^{0,+}$AT | Asc-1 | xCT | – |
| HGNC, UniProt | *SLC7A7*, Q9UM01 | *SLC7A6*, Q92536 | *SLC7A9*, P82251 | *SLC7A10*, Q9NS82 | *SLC7A11*, Q9UPY5 | *SLC7A13*, Q8TCU3 |
| Inhibitors | – | – | – | – | quisqualate ($pIC_{50}$ 5.3) [208] | – |

**Comments**: CAT4 appears to be non-functional in heterologous expression [792], while SLC7A14 has yet to be characterized.

Glycoprotein-associated amino acid transporters are 12 TM proteins, which heterodimerize with members of the SLC3 family to act as cell-surface amino acid exchangers.

Heterodimers between 4F2hc and LAT1 or LAT2 generate sodium-independent system L transporters. LAT1 transports large neutral amino acids including branched-chain and aromatic amino acids as well as miglustat, whereas LAT2 transports most of the neutral amino acids.

Heterodimers between 4F2hc and $y^+$LAT1 or $y^+$LAT2 generate transporters similar to the system $y^+L$ , which transport cationic (L-arginine, L-lysine, L-ornithine) amino acids independent of sodium and neutral (L-leucine, L-isoleucine, L-methionine, L-glutamine) amino acids in a partially sodium-dependent manner. These transporters are N-ethylmaleimide-insensitive. Heterodimers between rBAT and $b^{0,+}$AT appear to mediate sodium-independent system $b^{0,+}$ transport of most of the neutral amino acids and cationic amino acids (L-arginine, L-lysine and L-ornithine).

Asc-1 appears to heterodimerize with 4F2hc to allow the transport of small neutral amino acids (such as L-alanine, L-serine, L-threonine, L-glutamine and glycine), as well as D-serine, in a sodium-independent manner.

xCT generates a heterodimer with 4F2hc for a system $x^-_{e\text{-}c}$ transporter that mediates the sodium-independent exchange of L-cystine and L-glutamic acid.

AGT has been conjugated with SLC3 members as fusion proteins to generate functional transporters, but the identity of a native heterodimer has yet to be ascertained.

### Further reading on SLC7 family

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Kanai Y. (2021) Amino acid transporter LAT1 (SLC7A5) as a molecular target for cancer diagnosis and therapeutics. *Pharmacol Ther* 107964 [PMID:34390745]

Koppula P *et al.* (2020) Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. *Protein Cell* [PMID:33000412]

Lin W *et al.* (2020) SLC7A11/xCT in cancer: biological functions and therapeutic implications. *Am J Cancer Res* **10**: 3106-3126 [PMID:33163260]

**Further reading on SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)**

Bhutia YD *et al.* (2015) Amino Acid transporters in cancer and their relevance to "glutamine addiction": novel targets for the design of a new class of anticancer drugs. *Cancer Res* **75**: 1782-8 [PMID:25855379]

Fotiadis D *et al.* (2013) The SLC3 and SLC7 families of amino acid transporters. *Mol Aspects Med* **34**: 139-58 [PMID:23506863]

Palacín M *et al.* (2004) The ancillary proteins of HATs: SLC3 family of amino acid transporters. *Pflugers Arch* **447**: 490-4 [PMID:14770309]

Palacín M *et al.* (2005) The genetics of heteromeric amino acid transporters. *Physiology (Bethesda)* **20**: 112-24 [PMID:15772300]

Verrey F *et al.* (2004) CATs and HATs: the SLC7 family of amino acid transporters. *Pflugers Arch* **447**: 532-42 [PMID:14770310]

# SLC4 family of bicarbonate transporters

Transporters → SLC superfamily of solute carriers → SLC4 family of bicarbonate transporters

**Overview**: Together with the SLC26 family, the SLC4 family of transporters subserve anion exchange, principally of chloride and bicarbonate ($HCO_3^-$), but also carbonate and hydrogen sulphate ($HSO_4^-$). SLC4 family members regulate bicarbonate fluxes as part of carbon dioxide movement, chyme neutralization and reabsorption in the kidney.

Within the family, subgroups of transporters are identifiable: the electroneutral sodium-independent $Cl^-/HCO_3^-$ transporters (AE1, AE2 and AE3), the electrogenic sodium-dependent $HCO_3^-$ transporters (NBCe1 and NBCe2) and the electroneutral $HCO_3^-$ transporters (NBCn1 and NBCn2). Topographical information derives mainly from study of AE1, abundant in erythrocytes, which suggests a dimeric or tetrameric arrangement, with subunits made up of 13 TM domains and re-entrant loops at TM9/10 and TM11/12. The N terminus exhibits sites for interaction with multiple proteins, including glycolytic enzymes, haemoglobin and cytoskeletal elements.

# Anion exchangers

Transporters → SLC superfamily of solute carriers → SLC4 family of bicarbonate transporters → Anion exchangers

| | | | | |
|---|---|---|---|---|
| Nomenclature | Anion exchange protein 1 | Anion exchange protein 2 | Anion exchange protein 3 | Anion exchange protein 4 |
| Systematic nomenclature | SLC4A1 | SLC4A2 | SLC4A3 | SLC4A9 |
| Common abbreviation | AE1 | AE2 | AE3 | AE4 |
| HGNC, UniProt | *SLC4A1*, P02730 | *SLC4A2*, P04920 | *SLC4A3*, P48751 | *SLC4A9*, Q96Q91 |
| Endogenous substrates | $Cl^-$, $HCO_3^-$ | $Cl^-$, $HCO_3^-$ | $Cl^-$, $HCO_3^-$ | – |
| Stoichiometry | 1 $Cl^-$ (in) : 1 $HCO_3^-$ (out) | 1 $Cl^-$ (in) : 1 $HCO_3^-$ (out) | 1 $Cl^-$ (in) : 1 $HCO_3^-$ (out) | – |

# Sodium-dependent $HCO_3^-$ transporters

Transporters → SLC superfamily of solute carriers → SLC4 family of bicarbonate transporters → Sodium-dependent $HCO_3^-$ transporters

| Nomenclature | Electrogenic sodium bicarbonate cotransporter 1 | Electrogenic sodium bicarbonate cotransporter 4 | Electroneutral sodium bicarbonate cotransporter 1 | Electroneutral sodium bicarbonate cotransporter 2 | NBCBE | NaBC1 |
|---|---|---|---|---|---|---|
| Systematic nomenclature | SLC4A4 | SLC4A5 | SLC4A7 | SLC4A10 | SLC4A8 | SLC4A11 |
| Common abbreviation | NBCe1 | NBCe2 | NBCn1 | NBCn2 | NDCBE | BTR1 |
| HGNC, UniProt | *SLC4A4*, Q9Y6R1 | *SLC4A5*, Q9BY07 | *SLC4A7*, Q9Y6M7 | *SLC4A10*, Q6U841 | *SLC4A8*, Q2Y0W8 | *SLC4A11*, Q8NBS3 |
| Endogenous substrates | $NaHCO_3$ | $NaHCO_3$ | $NaHCO_3$ | $NaHCO_3$ | $Cl^-$, $NaHCO_3$ | $Cl^-$, $NaHCO_3$ |
| Stoichiometry | 1 $Na^+$ : 2/3 $HCO_3^-$ (out) or 1 $Na^+$ : $CO_3^{2*}$ | 1 $Na^+$ : 2/3 $HCO_3^-$ (out) or 1 $Na^+$ : $CO_3^{2*}$ | 1 $Na^+$ : 1 $HCO_3^-$ (out) or 1 $Na^+$ : $CO_3^{2*}$ | 1 $Na^+$ : 1 $HCO_3^-$ (out) or 1 Na : $CO_3^{2*}$ | 1 $Na^+$ : 2$HCO_3^-$ (in) : 1 $Cl^-$ (out) | – |

**Further reading on SLC4 family of bicarbonate transporters**


Majumdar D *et al.* (2010) Na-coupled bicarbonate transporters of the solute carrier 4 family in the nervous system: function, localization, and relevance to neurologic function. *Neuroscience* **171**: 951-72 [PMID:20884330]

Parker MD *et al.* (2013) The divergence, actions, roles, and relatives of sodium-coupled bicarbonate transporters. *Physiol Rev* **93**: 803-959 [PMID:23589833]

Reithmeier RA *et al.* (2016) Band 3, the human red cell chloride/bicarbonate anion exchanger (AE1, SLC4A1), in a structural context. *Biochim Biophys Acta* **1858**: 1507-32 [PMID:27058983]

Romero MF *et al.* (2013) The SLC4 family of bicarbonate ($HCO_3^-$) transporters. *Mol Aspects Med* **34**: 159-82 [PMID:23506864]

Thornell IM *et al.* (2015) Regulators of Slc4 bicarbonate transporter activity. *Front Physiol* **6**: 166 [PMID:26124722]


# SLC5 family of sodium-dependent glucose transporters

Transporters → SLC superfamily of solute carriers → SLC5 family of sodium-dependent glucose transporters

**Overview**: The SLC5 family of sodium-dependent glucose transporters includes, in mammals, the $Na^+$/substrate co-transporters for glucose (*e.g.* choline), D-glucose, monocarboxylates, *myo*-inositol and $I^-$ [221, 248, 795, 796]. Members of the SLC5 and SLC6 families, along with other unrelated $Na^+$ cotransporters (*i.e.* Mhp1 and BetP), share a common structural core that contains an inverted repeat of 5TM $\alpha$-helical domains [3].

# Hexose transporter family

Transporters → SLC superfamily of solute carriers → SLC5 family of sodium-dependent glucose transporters → Hexose transporter family

**Overview**: Detailed characterisation of members of the hexose transporter family is limited to SGLT1, 2 and 3, which are all inhibited in a competitive manner by phlorizin, a natural dihydrocholine glucoside, that exhibits modest selectivity towards SGLT2 (see [795] for an extensive review). SGLT1 is predominantly expressed in the small intestine, mediating the absorption of glucose (*e.g.* D-glucose), but also occurs in the brain, heart and in the late proximal straight tubule of the kidney. The expression of SGLT2 is almost exclusively restricted to the early proximal convoluted tubule of the kidney, where it is largely responsible for the renal reabsorption of glucose. SGLT3 is not a transporter but instead acts as a glucosensor generating an inwardly directed flux of $Na^+$ that causes membrane depolarization [170].

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | Sodium/glucose cotransporter 1 | Sodium/glucose cotransporter 2 | Low affinity sodium-glucose cotransporter | Sodium/glucose cotransporter 4 | Sodium/glucose cotransporter 5 |
| Systematic nomenclature | SLC5A1 | SLC5A2 | SLC5A4 | SLC5A9 | SLC5A10 |
| Common abbreviation | SGLT1 | SGLT2 | SGLT3 | SGLT4 | SGLT5 |
| HGNC, UniProt | *SLC5A1*, P13866 | *SLC5A2*, P31639 | *SLC5A4*, Q9NY91 | *SLC5A9*, Q2M3M2 | *SLC5A10*, A0PJK1 |
| Substrates | D-glucose [764], D-galactose [764], α-MDG [764] | α-MDG, D-glucose | 1-deoxynojirimycin-1-sulfonic acid [764], N-ethyl-1-deoxynojirimycin [764], 1-deoxynojirimycin [764], miglitol [764], miglustat [764], D-glucose [764] | D-glucose, α-MDG, D-mannose | D-glucose, D-galactose |
| Stoichiometry | 2 $Na^+$ : 1 glucose [389] | 1 $Na^+$ : 1 glucose [347] | – | – | – |
| Selective inhibitors | mizagliflozin ($pK_i$ 7.6) [356] | dapagliflozin ($pIC_{50}$ 9.3) [392] | – | – | – |
| Comments | – | – | SGLT3 acts as a glucosensor. | – | – |

**Comments**: Recognition and transport of substrate by SGLTs requires that the sugar is a pyranose. De-oxyglucose derivatives have reduced affinity for SGLT1, but the replacement of the sugar equatorial hydroxyl group by fluorine at some positions, excepting C2 and C3, is tolerated (see [795] for a detailed quantification). Although SGLT1 and SGLT2 have been described as high- and low-affinity sodium glucose co-transporters, respectively, recent work suggests that they have a similar affinity for glucose under physiological conditions [347]. Selective blockers of SGLT2, and thus blocking ~50% of renal glucose reabsorption, are in development for the treatment of diabetes (*e.g.* [113]).

# Choline transporter

Transporters → SLC superfamily of solute carriers → SLC5 family of sodium-dependent glucose transporters → Choline transporter

**Overview**: The high affinity, hemicholinium-3-sensitive, choline transporter (CHT) is expressed mainly in cholinergic neurones on nerve cell terminals and synaptic vesicles (keratinocytes being an additional location). In autonomic neurones, expression of CHT requires an activity-dependent retrograde signal from postsynaptic neurones [427]. Through recapture of choline generated by the hydrolysis of ACh by acetylcholinesterase, CHT serves to maintain acetylcholine synthesis within the presynaptic terminal [221]. Homozygous mice engineered to lack CHT die within one hour of birth as a result of hypoxia arising from failure of transmission at the neuromuscular junction of the skeletal muscles that support respiration [220]. A low affinity choline uptake mechanism that remains to be identified at the molecular level may involve multiple transporters. In addition, a family of choline transporter-like (CTL) proteins, (which are members of the SLC44 family) with weak $Na^+$ dependence have been described [728].

| | |
|---|---|
| Nomenclature | CHT |
| Systematic nomenclature | SLC5A7 |
| HGNC, UniProt | *SLC5A7*, Q9GZV3 |
| Substrates | triethylcholine |
| Endogenous substrates | choline |
| Stoichiometry | $Na^+$ : choline (variable stoichimetry); modulated by extracellular $Cl^-$ [367] |
| Selective inhibitors | hemicholinium-3 ($pK_i$ 7–8) [555] |
| Labelled ligands | [$^3$H]hemicholinium-3 ($pK_d$ 8.2–8.4) |

**Comments**: $K_i$and $K_D$ values for hemicholinium-3 listed in the table are for human CHT expressed in *Xenopus laevis* oocytes [556], or COS-7 cells [28]. Hemicholinium mustard is a substrate for CHT that causes covalent modification and irreversible inactivation of the transporter. Several exogenous substances (*e.g.* triethylcholine) that are substrates for CHT act as precursors to cholinergic false transmitters.

# Sodium iodide symporter, sodium-dependent multivitamin transporter and sodium-coupled monocarboxylate transporters

Transporters → SLC superfamily of solute carriers → SLC5 family of sodium-dependent glucose transporters → Sodium iodide symporter, sodium-dependent multivitamin transporter and sodium-coupled monocarboxylate transporters

**Overview**: The sodium-iodide symporter (NIS) is an iodide transporter found principally in the thyroid gland where it mediates the accumulation of $I^-$ within thyrocytes. Transport of $I^-$ by NIS from the blood across the basolateral membrane followed by apical efflux into the colloidal lumen, mediated at least in part by pendrin (SLC22A4), and most likely not SMCT1 (SLC5A8) as once thought, provides the $I^-$ required for the synthesis of the thyroid hormones triiodothyronine (triiodothyronine) and thyroxine ($T_4$) [69]. NIS is also expressed in the salivary glands, gastric mucosa, intestinal enterocytes and lactating breast. NIS mediates $I^-$ absorption in the intestine and $I^-$ secretion into the milk. SMVT is expressed on the apical membrane of intestinal enterocytes and colonocytes and is the main system responsible for biotin (vitamin H) and pantothenic acid (vitamin $B_5$) uptake in humans [630]. SMVT located in kidney proximal tubule epithelial cells mediates the reabsorption of biotin and pantothenic acid. SMCT1 (SLC5A8), which transports a wide range of monocarboxylates, is expressed in the apical membrane of epithelia of the small intestine, colon, kidney, brain neurones and the retinal pigment epithelium [248]. SMCT2 (SLC5A12) also localises to the apical membrane of kidney, intestine, and colon, but in the brain and retina is restricted to astrocytes and Müller cells, respectively [248]. SMCT1 is a high-affinity transporter whereas SMCT2 is a low-affinity transporter. The physiological substrates for SMCT1 and SMCT2 are lactate (L-lactic acid and D-lactic acid), pyruvic acid, propanoic acid, and nicotinic acid in non-colonic tissues such as the kidney. SMCT1 is also likely to be the principal transporter for the absorption of nicotinic acid (vitamin $B_3$) in the intestine and kidney [277]. In the small intestine and colon, the physiological substrates for these transporters are nicotinic acid and the short-chain fatty acids acetic acid, propanoic acid, and butyric acid that are produced by bacterial fermentation of dietary fiber [517]. In the kidney, SMCT2 is responsible for the bulk absorption of lactate because of its low-affinity/high-capacity nature. Absence of both transporters in the kidney leads to massive excretion of lactate in urine and consequently drastic decrease in the circulating levels of lactate in blood [716]. SMCT1 also functions as a tumour suppressor in the colon as well as in various other non-colonic tissues [249]. The tumour-suppressive function of SMCT1 is based on its ability to transport pyruvic acid, an inhibitor of histone deacetylases, into cells in non-colonic tissues [717]; in the colon, the ability of SMCT1 to transport butyric acid and propanoic acid, also inhibitors of histone deacetylases, underlies the tumour-suppressive function of this transporter [248, 249, 309]. The ability of SMCT1 to promote histone acetylase inhibition through accumulation of butyric acid and propanoic acid in immune cells is also responsible for suppression of dendritic cell development in the colon [667].

| | | | | |
|---|---|---|---|---|
| Nomenclature | NIS | SMVT | SMCT1 | SMCT2 |
| Systematic nomenclature | SLC5A5 | SLC5A6 | SLC5A8 | SLC5A12 |
| HGNC, UniProt | *SLC5A5*, Q92911 | *SLC5A6*, Q9Y289 | *SLC5A8*, Q8N695 | *SLC5A12*, Q1EHB4 |
| Substrates | pertechnetate, $ClO_4^-$, $SCN^-$, $I^-$, $NO_3^-$ | pantothenic acid [156], biotin [156], lipoic acid [156], $I^-$ [156] | β-L-hydroxybutyric acid, acetic acid, butyric acid, propanoic acid, nicotinic acid, β-D-hydroxybutyric acid, L-lactic acid, D-lactic acid, salicylic acid, 3-bromopyruvate, dichloroacetate, 2-oxothiazolidine-4-carboxylate, acetoacetic acid, benzoate, 5-aminosalicylate, α-ketoisocaproate, pyroglutamic acid, γ-hydroxybutyric acid, pyruvic acid | nicotinic acid, L-lactic acid, pyruvic acid |
| Stoichiometry | $2Na^+ : 1\ I^-$ [205]; $1Na^+ : 1\ ClO_4^-$ [175] | $2Na^+$ : 1 biotin (or pantothenic acid) [587] | $2Na^+$ : 1 monocarboxylate [135] | – |
| Inhibitors | – | – | fenoprofen ($pIC_{50}$ 4.6) [364], ibuprofen ($pIC_{50}$ 4.2) [364], ketoprofen ($pIC_{50}$ 3.9) [364] | – |
| Comments | – | – | – | Lactate/SLC5A12-induced reprogramming of CD4+ T cells (and he resulting induction of pro-inflammatory IL-17) has been shown to be amenable to pharmacological modulation in a mouse model of arthritis, and is proposed as a therapeutic target for chronic inflammatory disorders. |

**Comments**: $I^-$, $ClO_4^-$, thiocyanate and $NO_3^-$ are competitive substrate inhibitors of NIS [175]. Lipoic acid appears to act as a competitive substrate inhibitor of SMVT [769] and the anticonvulsant drugs primidone and carbamazepine competitively block the transport of biotin by brush border vesicles prepared from human intestine [631].

# Sodium *myo*-inositol cotransporter transporters

Transporters → SLC superfamily of solute carriers → SLC5 family of sodium-dependent glucose transporters → Sodium *myo*-inositol cotransporter transporters

**Overview**: Three different mammalian myo-inositol cotransporters are currently known; two are the $Na^+$-coupled SMIT1 and SMIT2 tabulated below and the third is proton-coupled HMIT (SLC2A13). SMIT1 and SMIT2 have a widespread and overlapping tissue location but in polarized cells, such as the Madin-Darby canine kidney cell line, they segregate to the basolateral and apical membranes, respectively [68]. In the nephron, SMIT1 mediates *myo*-inositol uptake as a 'compatible osmolyte' when inner medullary tubules are exposed to increases in extracellular osmolality, whilst SMIT2 mediates the reabsorption of *myo*-inositol from the filtrate. In some species (*e.g.* rat, but not rabbit) apically located SMIT2 is responsible for the uptake of *myo*-inositol from the intestinal lumen [27].

| | | |
|---|---|---|
| Nomenclature | SMIT | SGLT6 |
| Systematic nomenclature | SLC5A3 | SLC5A11 |
| Common abbreviation | SMIT1 | SMIT2 |
| HGNC, UniProt | *SLC5A3*, P53794 | *SLC5A11*, Q8WWX8 |
| Substrates | *myo*-inositol, *scyllo*-inositol > L-fucose > L-xylose > L-glucose, D-glucose, α-MDG > D-galactose, D-fucose > D-xylose [312] | *myo*-inositol = D-*chiro*-inositol> D-glucose > D-xylose > L-xylose [136] |
| Stoichiometry | 2 $Na^+$ :1 *myo*-inositol [312] | 2 $Na^+$ :1 *myo*-inositol [83] |
| Inhibitors | phlorizin [136] | phlorizin ($pK_i$ 4.1) [136] |

**Comments**: The data tabulated are those for dog SMIT1 and rabbit SMIT2. SMIT2 transports D-*chiro*-inositol, but SMIT1 does not. In addition, whereas SMIT1 transports both D-xylose and L-xylose and D-fucose and L-fucose, SMIT2 transports only the D-isomers of these sugars [136, 312]. Thus the substrate specificities of SMIT1 (for L-fucose) and SMIT2 (for D-*chiro*-inositol) allow discrimination between the two SMITs. Human SMIT2 appears not to transport glucose [461].

### Further reading on SLC5 family of sodium-dependent glucose transporters


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Gyimesi G *et al.* (2020) Sodium-coupled glucose transport, the SLC5 family, and therapeutically relevant inhibitors: from molecular discovery to clinical application. *Pflugers Arch* **472**: 1177-1206 [PMID:32767111]

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Lehmann A *et al.* (2016) Intestinal SGLT1 in metabolic health and disease. *Am J Physiol Gastrointest Liver Physiol* **310**: G887-98 [PMID:27012770]

Wright EM. (2013) Glucose transport families SLC5 and SLC50. *Mol Aspects Med* **34**: 183-96 [PMID:23506865]

Wright EM *et al.* (2011) Biology of human sodium glucose transporters. *Physiol Rev* **91**: 733-94 [PMID:21527736]


# SLC6 neurotransmitter transporter family

Transporters → SLC superfamily of solute carriers → SLC6 neurotransmitter transporter family

**Overview**: Members of the solute carrier family 6 (SLC6) of sodium- and (sometimes chloride-) dependent neurotransmitter transporters [11, 92, 119, 428] are primarily plasma membrane located and may be divided into four subfamilies that transport monoamines, GABA, glycine and neutral amino acids, plus the related bacterial NSS transporters [632]. The members of this superfamily share a structural motif of 10 TM segments that has been observed in crystal structures of the NSS bacterial homolog $LeuT_{Aa}$, a $Na^+$-dependent amino acid transporter from *Aquiflex aeolicus* [818] and in several other transporter families structurally related to LeuT [231].

# Monoamine transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC6 neurotransmitter transporter family → Monoamine transporter subfamily

**Overview**: Monoamine neurotransmission is limited by perisynaptic transporters. Presynaptic monoamine transporters allow recycling of synaptically released noradrenaline, dopamine and 5-hydroxytryptamine.

| | | | |
|---|---|---|---|
| Nomenclature | NET | DAT | SERT |
| Systematic nomenclature | SLC6A2 | SLC6A3 | SLC6A4 |
| HGNC, UniProt | *SLC6A2*, P23975 | *SLC6A3*, Q01959 | *SLC6A4*, P31645 |
| Substrates | $MPP^+$, methamphetamine, amphetamine | $MPP^+$, amphetamine, methamphetamine | MDMA, p-chloroamphetamine |
| Endogenous substrates | (-)-noradrenaline, dopamine, (-)-adrenaline | (-)-noradrenaline, dopamine, (-)-adrenaline | 5-hydroxytryptamine |
| Stoichiometry | 1 noradrenaline: 1 $Na^+$:1 $Cl^-$ [301] | 1 dopamine: 1-2 $Na^+$: 1 $Cl^-$ [300] | 1 5-HT:1 $Na^+$:1 $Cl^-$ (in), + 1 $K^+$ (out) [697] |
| Inhibitors | H05 ($pK_i$ 8.2) [811] – Rat | – | H05 ($pK_i$ 8.3) [811] – Rat |
| Sub/family-selective inhibitors | sibutramine ($pK_i$ 5.2) [38] | sibutramine ($pK_i$ 6.3) [38] | sibutramine ($pK_i$ 6) [38] |
| Selective inhibitors | mazindol ($pK_i$ 8.9), protriptyline ($pIC_{50}$ 8.8) [519], nisoxetine ($pK_i$ 8.4), protriptyline ($pK_i$ 8.2) [464], nomifensine ($pK_i$ 8.1), reboxetine ($pK_i$ 8) [793] | mazindol ($pK_i$ 8), WIN35428 ($pK_i$ 7.9) [605], GBR12935 ($pK_i$ 7.6), dexmethylphenidate ($pK_i$ 7.6) [437], methylphenidate ($pIC_{50}$ 7.1) [236] | clomipramine ($pK_i$ 9.7) [707], paroxetine ($pK_i$ 9.6) [707], clomipramine ($pK_d$ 9.6) [707], sertraline ($pK_i$ 9.1), escitalopram ($pIC_{50}$ 9) [619], dapoxetine ($pIC_{50}$ 8.9) [260], fluvoxamine ($pK_d$ 8.7) [707], fluoxetine ($pK_i$ 8.5) [707], citalopram ($pK_i$ 8.4) [58] |
| Labelled ligands | [$^3$H]mazindol (Inhibitor) ($pK_d$ 9.3) [595] – Rat, [$^3$H] nisoxetine (Inhibitor) ($pK_d$ 8.4) | [$^3$H]GBR12935 (Inhibitor) ($pK_d$ 8.5) [589], [$^3$H] WIN35428 (Inhibitor) ($pK_d$ 8) [589] | [$^3$H]paroxetine (Inhibitor) ($pK_d$ 9.7), [$^3$H]citalopram (Inhibitor) ($pK_d$ 8.3) |

**Comments**: [$^{125}$I]RTI55 labels all three monoamine transporters (NET, DAT and SERT) with affinities between 0.5 and 5 nM. Cocaine is an inhibitor of all three transporters with $pK_i$ values between 6.5 and 7.2. Potential alternative splicing sites in non-coding regions of SERT and NET have been identified. A bacterial homologue of SERT shows allosteric modulation by selected anti-depressants [668].

# GABA transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC6 neurotransmitter transporter family → GABA transporter subfamily

**Overview**: The activity of GABA-transporters located predominantly upon neurones (GAT-1), glia (GAT-3) or both (GAT-2, BGT-1) serves to terminate phasic GABA-ergic transmission, maintain low ambient extracellular concentrations of GABA, and recycle GABA for reuse by neurones. Nonetheless, ambient concentrations of GABA are sufficient to sustain tonic inhibition mediated by high affinity $GABA_A$ receptors in certain neuronal populations [653]. GAT1 is the predominant GABA transporter in the brain and occurs primarily upon the terminals of presynaptic neurones and to a much lesser extent upon distal astocytic processes that are in proximity to axons terminals. GAT3 resides predominantly on distal astrocytic terminals that are close to the GABAergic synapse. By contrast, BGT1 occupies an extrasynaptic location possibly along with GAT2 which has limited expression in the brain [485]. TauT is a high affinity taurine transporter involved in osmotic balance that occurs in the brain and non-neuronal tissues, such as the kidney, brush border membrane of the intestine and blood brain barrier [119, 321]. CT1, which transports creatine, has a ubiquitous expression pattern, often co-localizing with creatine kinase [119].

| Nomenclature | GAT1 | GAT2 | GAT3 | BGT1 | TauT | CT1 |
|---|---|---|---|---|---|---|
| Systematic nomenclature | SLC6A1 | SLC6A13 | SLC6A11 | SLC6A12 | SLC6A6 | SLC6A8 |
| HGNC, UniProt | *SLC6A1*, P30531 | *SLC6A13*, Q9NSD5 | *SLC6A11*, P48066 | *SLC6A12*, P48065 | *SLC6A6*, P31641 | *SLC6A8*, P48029 |
| Substrates | nipecotic acid, guvacine | nipecotic acid, guvacine | nipecotic acid, guvacine | – | – | – |
| Endogenous substrates | GABA | GABA, β-alanine | GABA, β-alanine | GABA, betaine | GABA [21], β-alanine, taurine | creatine |
| Stoichiometry | $2Na^+$: $1Cl^-$: 1GABA | $2Na^+$: $1Cl^-$:1GABA | ≥ $2Na^+$: 2 $Cl^-$: 1GABA | $3Na^+$: 1 (or 2) $Cl^-$: 1GABA | $2Na^+$: $1Cl^-$: 1 taurine | Probably $2Na^+$: $1Cl^-$: 1 creatine |
| Selective inhibitors | NNC-711 ($pIC_{50}$ 7.4) [78], tiagabine ($pIC_{50}$ 7.2) [78], SKF89976A ($pIC_{50}$ 6.9) [166], CI-966 ($pIC_{50}$ 6.6) [78], (R/S) EF-1500 ($pIC_{50}$ 4.9–5.7), (R)-EF-1520 ($pIC_{50}$ 5.1–5.4), LU32-176B ($pIC_{50}$ 5.4) [787] – Mouse, (S)-EF-1520 ($pIC_{50}$ 3.6–3.9) | SNAP-5114 ($pIC_{50}$ 4.7) [77] – Rat | SNAP-5114 ($pIC_{50}$ 5.2) [77] | NNC052090 ($pK_i$ 5.9) [721] – Mouse, (R/S) EF-1500 ($pIC_{50}$ 4.9), (R)-EF-1520 ($pIC_{50}$ 3.7–4.7), (S)-EF-1520 ($pIC_{50}$ 3.6–4.5), LU32-176B ($pIC_{50}$ 4) [787] – Mouse | – | – |
| Labelled ligands | [$^3$H]tiagabine (Inhibitor) | – | – | – | – | – |

**Comments**: The $IC_{50}$ values for GAT1-4 reported in the table reflect the range reported in the literature from studies of both human and mouse transporters. There is a tendency towards lower $IC_{50}$ values for the human orthologue [433]. SNAP-5114 is only weakly selective for GAT 2 and GAT3, with $IC_{50}$ values in the range 22 to >30 μM at GAT1 and BGT1, whereas NNC052090 has at least an order of magnitude selectivity for BGT1 [see [134, 649] for reviews]. Compound (R)-4d is a recently described compound that displays 20-fold selectivity for GAT3 over GAT1 [241]. In addition to the inhibitors listed, deramciclane is a moderately potent, though non-selective, inhibitor of all cloned GABA transporters ($IC_{50}$ = 26-46 μM; [165]). Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine that potently inhibit the uptake of [$^3$H]GABA into rat synaptosomes have been described [409]. Several derivatives of exo-THPO (*e.g.* N-methyl-exo-THPO and N-acetyloxyethyl-exo-THPO) demonstrate selectivity as blockers of astroglial, versus neuronal, uptake of GABA [see [134, 648] for reviews]. GAT3 is inhibited by physiologically relevant concentrations of $Zn^{2+}$ [138]. Taut transports GABA, but with low affinity, but CT1 does not, although it can be engineered to do so by mutagenesis guided by LeuT as a structural template [173]. Although inhibitors of creatine transport by CT1 (*e.g.* β-guanidinopropionic acid, cyclocreatine, guanidinoethane sulfonic acid) are known (*e.g.* [148]) they insufficiently characterized to be included in the table.

# Glycine transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC6 neurotransmitter transporter family → Glycine transporter subfamily

**Overview**: Two gene products, GlyT1 and GlyT2, are known that give rise to transporters that are predominantly located on glia and neurones, respectively. Five variants of GlyT1 (a,b,c,d & e) differing in their N- and C-termini are generated by alternative promoter usage and splicing, and three splice variants of GlyT2 (a,b & c) have also been identified (see [61, 209, 272, 686] for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission [59, 242], but also are important, in early neonatal life, for regulating glycine concentrations at inhibitory glycinergic synapses [273]. Homozygous mice engineered to totally lack GlyT1 exhibit severe respiratory and motor deficiencies due to hyperactive glycinergic signalling and die within the first postnatal day [273, 730]. Disruption of GlyT1 restricted to forebrain neurones is associated with enhancement of EPSCs mediated by NMDA receptors and behaviours that are suggestive of a promnesic action [827]. GlyT2 transporters localised on the axons and boutons of glycinergic neurones appear crucial for efficient transmitter loading of synaptic vesicles but may not be essential for the termination of inhibitory neurotransmission [274, 621]. Mice in which GlyT2 has been deleted develop a fatal hyperekplexia phenotype during the second postnatal week [274] and mutations in the human gene encoding GlyT2 (SLC6A5) have been identified in patients with hyperekplexia (reviewed by [323]). $ATB^{0+}$ (SLC6A14) is a transporter for numerous dipolar and cationic amino acids and thus has a much broader substrate specificity than the glycine transporters alongside which it is grouped on the basis of structural similarity [119]. $ATB^{0+}$ is expressed in various peripheral tissues [119]. By contrast PROT (SLC6A7), which is expressed only in brain in association with a subset of excitatory nerve terminals, shows specificity for the transport of L-proline.

| | | | | |
|---|---|---|---|---|
| Nomenclature | GlyT1 | GlyT2 | $ATB^{0,+}$ | PROT |
| Systematic nomenclature | SLC6A9 | SLC6A5 | SLC6A14 | SLC6A7 |
| HGNC, UniProt | *SLC6A9*, P48067 | *SLC6A5*, Q9Y345 | *SLC6A14*, Q9UN76 | *SLC6A7*, Q99884 |
| Substrates | – | – | zwitterionic or cationic NOS inhibitors [326], valganciclovir [740], 1-methyltryptophan [394], BCH | – |
| Endogenous substrates | glycine, sarcosine | glycine | $\beta$-alanine [19, 21]<br>L-isoleucine > L-leucine, L-methionine > L-phenylalanine > L-tryptophan > L-valine > L-serine [669] | L-proline |
| Stoichiometry | 2 $Na^+$: 1 $Cl^-$: 1 glycine | 3 $Na^+$: 1 $Cl^-$: 1 glycine | 2-3 $Na^+$: 1 $Cl^-$: 1 amino acid [669] | Probably 2 $Na^+$: 1 $Cl^-$: 1 L-proline |
| Inhibitors | PF-03463275 ($pK_i$ 7.9) [474] | GT-0198 ($pIC_{50}$ 8.8) [557], opiranserin ($pIC_{50}$ 6.1) [553], bitopertin ($pEC_{50}$ <4.5) [579] | – | – |
| Selective inhibitors | (R)-NFPS ($pIC_{50}$ 8.5–9.1) [575], SSR-103800 ($pIC_{50}$ 8.7) [82], N-methyl-SSR504734 ($pIC_{50}$ 8.6), LY2365109 ($pIC_{50}$ 7.8) [575], GSK931145 ($pIC_{50}$ 7.6), bitopertin ($pEC_{50}$ 7.5) [579] | Org 25543 ($pIC_{50}$ 7.8) [108], ALX 1393 ($pIC_{50}$ 7) [509], ALX 1405 | $\alpha$-methyl-D,L-tryptophan ($pIC_{50}$ 3.6) [394] | compound 58 ($pIC_{50}$ 7.7) [858], LP-403812 ($pIC_{50}$ 7) [830] |
| Labelled ligands | [$^3$H](R)-NPTS (Binding) ($pK_d$ 9) [473], [$^3$H] GSK931145 (Binding) ($pK_d$ 8.8) [331], [$^{35}$S]ACPPB (Binding) ($pK_d$ 8.7) [836], [$^3$H]SB-733993 (Binding) ($pK_d$ 8.7) [331], [$^3$H]N-methyl-SSR504734 ($pK_d$ 8.1–8.5), [$^3$H]NFPS ($pK_d$ 7.7–8.2) | – | – | – |
| Comments | – | N-Oleoyl-L-carnitine (0.3$\mu$M, [104]) and and N-arachidonoylglycine ($IC_{50}$ 5-8 $\mu$M, [788]) have been described as potential endogenous selective GlyT2 inhibitors | – | – |

**Comments**: Sarcosine is a selective transportable inhibitor of GlyT1 and also a weak agonist at the glycine binding site of the NMDA receptor [840], but has no effect on GlyT2. This difference has been attributed to a single glycine residue in TM6 (serine residue in GlyT2) [750]. Inhibition of GLYT1 by the sarcosine derivatives NFPS, NPTS and Org 24598 is non-competitive [490, 503]. $IC_{50}$ values for Org 24598 reported in the literature vary, most likely due to differences in assay conditions [95, 490]. The tricyclic antidepressant amoxapine weakly inhibits GlyT2 ($IC_{50}$ 92 $\mu$M) with approximately 10-fold selectivity over GlyT1 [549]. The endogenous lipids arachidonic acid and anandamide exert opposing effects upon GlyT1a, inhibiting ($IC_{50}$~ 2 $\mu$M) and potentiating ($EC_{50}$ ~ 13 $\mu$M) transport currents, respectively [570]. N-arachidonyl-glycine, N-arachidonyl-$\gamma$-aminobutyric acid and N-arachidonyl-D-alanine have been described as endogenous non-competitive inhibitors of GlyT2a, but not GlyT1b [189, 372, 788]. Protons [37] and $Zn^{2+}$ [380] act as non-competitive inhibitors of GlyT1b, with $IC_{50}$ values of ~100 nM and ~10 $\mu$M respectively, but neither ion affects GlyT2 (reviewed by [748]). Glycine transport by GLYT1 is inhibited by $Li^+$, whereas GLYT2 transport is stimulated (both in the presence of $Na^+$) [571].

# Neutral amino acid transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC6 neurotransmitter transporter family → Neutral amino acid transporter subfamily

**Overview**: Certain members of neutral amino acid transport family are expressed upon the apical surface of epithelial cells and are important for the absorption of amino acids from the duodenum, jejunum and ileum and their reabsorption within the proximal tubule of the nephron (*i.e.* $B^0AT1$ (SLC6A19), SLC6A18, SLC6A20). Others may function as transporters for neurotransmitters or their precursors (*i.e.* $B^0AT2$, SLC6A17) [93]. $B^0AT1$ has been proposed as a drug target to treat phenylketonuria [56].

| | | | | | | |
|---|---|---|---|---|---|---|
| Nomenclature | $B^0AT1$ | $B^0AT2$ | $B^0AT3$ | NTT5 | NTT4 | SIT1 |
| Systematic nomenclature | SLC6A19 | SLC6A15 | SLC6A18 | SLC6A16 | SLC6A17 | SLC6A20 |
| HGNC, UniProt | *SLC6A19*, Q695T7 | *SLC6A15*, Q9H2J7 | *SLC6A18*, Q96N87 | *SLC6A16*, Q9GZN6 | *SLC6A17*, Q9H1V8 | *SLC6A20*, Q9NP91 |
| Endogenous substrates | L-leucine, L-methionine, L-isoleucine, L-valine > L-asparagine, L-phenylalanine, L-alanine, L-serine > L-threonine, glycine, L-proline [92] | L-proline > L-alanine, L-valine, L-methionine, L-leucine > L-isoleucine, L-threonine, L-asparagine, L-serine, L-phenylalanine > glycine [92] | L-alanine, glycine > L-methionine, L-phenylalanine, L-leucine, L-histidine, L-glutamine [753] | – | L-leucine, L-methionine, L-proline > L-cysteine, L-alanine, L-glutamine, L-serine > L-histidine, glycine [833] | L-proline |
| Stoichiometry | 1 $Na^+$: 1 amino acid [76] | 1 $Na^+$: 1 amino acid [90] | $Na^+$- and $Cl^-$ -dependent transport [666] | – | $Na^+$-dependent, $Cl^-$-independent transport [833] | 2 $Na^+$: 1 $Cl^-$: 1 imino acid [88] |
| Inhibitors | cinromide ($pIC_{50}$ 6.4) [151], inhibitor E18 ($pIC_{50}$ 5.5) [813], inhibitor CB3 ($pIC_{50}$ 5.3) [813], inhibitor E4 ($pIC_{50}$ 5.1) [813], nimesulide ($pIC_{50}$ 4.6) [581] – Rat, benzatropine ($pIC_{50}$ 4.4) [126] | – | – | – | – | – |
| Selective inhibitors | – | loratadine ($pIC_{50}$ 5.4) [145] | – | – | – | – |
| Comments | Mutations in $B^0AT1$ are associated with Hartnup disorder | – | SLC6A18 is a functional transporter in mouse, but not in humans. | – | – | – |

**Further reading on SLC6 neurotransmitter transporter family**


Bermingham DP *et al.* (2016) Kinase-dependent Regulation of Monoamine Neurotransmitter Transporters. *Pharmacol Rev* **68**: 888-953 [PMID:27591044]

Bröer S *et al.* (2012) The solute carrier 6 family of transporters. *Br J Pharmacol* **167**: 256-78 [PMID:22519513]

Colas C. (2020) Toward a Systematic Structural and Functional Annotation of Solute Carriers Transporters-Example of the SLC6 and SLC7 Families. *Front Pharmacol* **11**: 1229 [PMID:32973497]

Joncquel-Chevalier Curt M *et al.* (2015) Creatine biosynthesis and transport in health and disease. *Biochimie* **119**: 146-65 [PMID:26542286]

Lohr KM *et al.* (2017) Membrane transporters as mediators of synaptic dopamine dynamics: implications for disease. *Eur J Neurosci* **45**: 20-33 [PMID:27520881]

Schumann-Gillett A *et al.* (2019) Is protein structure enough? A review of the role of lipids in SLC6 transporter function. *Neurosci Lett* **700**: 64-69 [PMID:29758303]

# SLC8 family of sodium/calcium exchangers

Transporters → SLC superfamily of solute carriers → SLC8 family of sodium/calcium exchangers

**Overview**: The sodium/calcium exchangers (NCX) use the extracellular sodium concentration to facilitate the extrusion of calcium out of the cell. Alongside the plasma membrane $Ca^{2+}$-ATPase (PMCA) and sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA), as well as the sodium/potassium/calcium exchangers (NKCX, SLC24 family), NCX allow recovery of intracellular calcium back to basal levels after cellular stimulation. When intracellular sodium ion levels rise, for example, following depolarisation, these transporters can operate in the reverse direction to allow calcium influx and sodium efflux, as an electrogenic mechanism. Structural modelling suggests the presence of 9 TM segments, with a large intracellular loop between the fifth and sixth TM segments [11].

| | | | |
|---|---|---|---|
| Nomenclature | Sodium/calcium exchanger 1 | Sodium/calcium exchanger 2 | Sodium/calcium exchanger 3 |
| Systematic nomenclature | SLC8A1 | SLC8A2 | SLC8A3 |
| Common abbreviation | NCX1 | NCX2 | NCX3 |
| HGNC, UniProt | *SLC8A1*, P32418 | *SLC8A2*, Q9UPR5 | *SLC8A3*, P57103 |
| Stoichiometry | 3 $Na^+$ (in) : 1 $Ca^{2+}$ (out) or 4 $Na^+$ (in) : 1 $Ca^{2+}$ (out) [176]; Reverse mode 1 $Ca^{2+}$ (in): 1 $Na^+$ (out) | – | – |
| Activators | neurounina-1 ($pEC_{50}$ 8.9) [520] – Dog | neurounina-1 ($pEC_{50}$ 8.8) [520] – Rat | – |
| Selective inhibitors | – | – | YM-244769 ($pIC_{50}$ 7.7) [368] |

**Comments**: Although subtype-selective inhibitors of NCX function are not widely available, 3,4-dichlorobenzamil and CBDMB act as non-selective NCX inhibitors, while SEA0400, KB-R7943, SN6, ORM-10103 [379] and ORM-10962 [419] act to inhibit NCX function with varying degrees of selectivity. BED is a preferential NCX3 inhibitor. It inhibits both modes of NCX3 operation, but only the reverse mode of NCX2 (and with reduced potency compared to NCX3) [650]. YM-244769 inhibits NCX3 preferentially over other isoforms [368, 819]. Neurounina-1 stimulates NCX1 and NCX2 activity but not that of NCX3 [520].

### Further reading on SLC8 family of sodium/calcium exchangers

Giladi M *et al.* (2016) Structure-Functional Basis of Ion Transport in Sodium-Calcium Exchanger (NCX) Proteins. *Int J Mol Sci* **17**: [PMID:27879668]

Khananshvili D. (2013) The SLC8 gene family of sodium-calcium exchangers (NCX) - structure, function, and regulation in health and disease. *Mol Aspects Med* **34**: 220-35 [PMID:23506867]

Sekler I. (2015) Standing of giants shoulders the story of the mitochondrial Na(+)Ca(2+) exchanger. *Biochem Biophys Res Commun* **460**: 50-2 [PMID:25998733]

# SLC9 family of sodium/hydrogen exchangers

Transporters → SLC superfamily of solute carriers → SLC9 family of sodium/hydrogen exchangers

**Overview**: Sodium/hydrogen exchangers or sodium/proton antiports are a family of transporters that maintain cellular pH by utilising the sodium gradient across the plasma membrane to extrude protons produced by metabolism, in a stoichiometry of 1 $Na^+$ (in) : 1 $H^+$ (out). Several isoforms, NHE6, NHE7, NHE8 and NHE9 appear to locate on intracellular membranes [518, 530, 548]. $Li^+$ and $NH_4^+$, but not $K^+$, ions may also be transported by some isoforms. Modelling of the topology of these transporters indicates 12 TM regions with an extended intracellular C-terminus containing multiple regulatory sites. NHE1 is considered to be a ubiquitously-expressed 'housekeeping' transporter. NHE3 is highly expressed in the intestine and kidneys and regulate sodium movements in those tissues. NHE10 is present in sperm [768] and osteoclasts [448]; gene disruption results in infertile male mice [768].

Information on members of this family may be found in the online database.

**Comments**: Analogues of the non-selective cation transport inhibitor amiloride appear to inhibit NHE function through competitive inhibition of the extracellular $Na^+$ binding site. The more selective amiloride analogues MPA and ethylisopropylamiloride exhibit a rank order of affinity of inhibition of NHE1 > NHE2 > NHE3 [142, 731, 732].

**Further reading on SLC9 family of sodium/hydrogen exchangers**

Donowitz M *et al.* (2013) SLC9/NHE gene family, a plasma membrane and organellar family of $Na^+/H^+$ exchangers. *Mol Aspects Med* **34**: 236-51 [PMID:23506868]
Kato A *et al.* (2011) Regulation of electroneutral NaCl absorption by the small intestine. *Annu Rev Physiol* **73**: 261-81 [PMID:21054167]
Ohgaki R *et al.* (2011) Organellar Na+/H+ exchangers: novel players in organelle pH regulation and their emerging functions. *Biochemistry* **50**: 443-50 [PMID:21171650]
Parker MD *et al.* (2015) Na+-H+ exchanger-1 (NHE1) regulation in kidney proximal tubule. *Cell Mol Life Sci* **72**: 2061-74 [PMID:25680790]
Ruffin VA *et al.* (2014) Intracellular pH regulation by acid-base transporters in mammalian neurons. *Front Physiol* **5**: 43 [PMID:24592239]

# SLC10 family of sodium-bile acid co-transporters

Transporters → SLC superfamily of solute carriers → SLC10 family of sodium-bile acid co-transporters

**Overview**: The SLC10 family transport bile acids, sulphated solutes, and other xenobiotics in a sodium-dependent manner. The founding members, SLC10A1 (NTCP) and SLC10A2 (ASBT) function, along with members of the ABC transporter family (MDR1/ABCB1, BSEP/ABCB11 and MRP2/ABCC2) and the organic solute transporter obligate heterodimer OST$\alpha$:OST$\beta$ (SLC51), to maintain the enterohepatic circulation of bile acids [155, 407]. SLC10A6 (SOAT) functions as a sodium-dependent transporter of sulphated solutes including sulfphated steroids and bile acids [261, 263]. Transport function has not yet been demonstrated for the 4 remaining members of the SLC10 family, SLC10A3 (P3), SLC10A4 (P4), SLC10A5 (P5), and SLC10A7 (P7), and the identity of their endogenous substrates remain unknown [222, 263, 271, 762]. Members of the SLC10 family are predicted to have seven transmembrane domains with an extracellular N-terminus and cytoplasmic C-terminus [49, 315].

| | | | |
|---|---|---|---|
| Nomenclature | Sodium/bile acid and sulphated solute cotransporter 1 | Sodium/bile acid and sulphated solute cotransporter 2 | Sodium/bile acid and sulphated solute cotransporter 6 |
| Systematic nomenclature | SLC10A1 | SLC10A2 | SLC10A6 |
| Common abbreviation | NTCP | ASBT | SOAT |
| HGNC, UniProt | *SLC10A1*, Q14973 | *SLC10A2*, Q12908 | *SLC10A6*, Q3KNW5 |
| Substrates | – | glycodeoxycholic acid > glycoursodeoxycholic acid, glycochenodeoxycholic acid > taurocholic acid > cholic acid [144] | dehydroepiandrosterone sulphate [263], pregnenolone sulphate [261], taurolithocholic acid-3-sulphate, estrone-3-sulphate |
| Endogenous substrates | estrone-3-sulphate, dehydroepiandrosterone sulphate [144, 222, 497], iodothyronine sulphates [762] tauroursodeoxycholic acid, taurocholic acid, taurochenodeoxycholic acid > glycocholic acid > cholic acid [497] | – | – |
| Stoichiometry | 2 $Na^+$: 1 bile acid [49, 261] | >1 $Na^+$: 1 bile acid [144, 782] | – |
| Inhibitors | (-)-propranolol ($pIC_{50}$ 8.2) [404], cyclosporin A ($pIC_{50}$ 6) [404], ursodeoxycholic acid ($pIC_{50}$ 5.4) [404], (+)-propranolol ($pIC_{50}$ 5.3) [404], cyclosporin A ($pK_i$ 5.1) [177], irbesartan ($pK_i$ 4.9) [177] | odevixibat ($pIC_{50}$ 9.8) [264], maralixibat ($pIC_{50}$ 9.6) [345], elobixibat ($pIC_{50}$ 8.9) [265], SC-435 ($pIC_{50}$ 8.8) [64], 264W94 ($pIC_{50}$ 7.3) [724, 803] | – |
| Labelled ligands | – | [$^3$H]taurocholic acid [144] | – |
| Comments | – | Chenodeoxycholyl-N$\epsilon$-nitrobenzoxadiazol-lysine is a fluorescent bile acid analogue used as a probe [782]. | – |

**Comments**: Heterologously expressed SLC10A4 [262] or SLC10A7 [271] failed to exhibit significant transport of taurocholic acid, pregnenolone sulphate, dehydroepiandrosterone sulphate or choline. SLC10A4 has recently been suggested to associate with neuronal vesicles [97].

**Further reading on SLC10 family of sodium-bile acid co-transporters**

Anwer MS *et al.* (2014) Sodium-dependent bile salt transporters of the SLC10A transporter family: more than solute transporters. *Pflugers Arch* **466**: 77-89 [PMID:24196564]
Claro da Silva T *et al.* (2013) The solute carrier family 10 (SLC10): beyond bile acid transport. *Mol Aspects Med* **34**: 252-69 [PMID:23506869]
Dawson PA. (2017) Roles of Ileal ASBT and OST$\alpha$-OST$\beta$ in Regulating Bile Acid Signaling. *Dig Dis* **35**: 261-266 [PMID:28249269]
Zwicker BL *et al.* (2013) Transport and biological activities of bile acids. *Int J Biochem Cell Biol* **45**: 1389-98 [PMID:23603607]

# SLC11 family of proton-coupled metal ion transporters

Transporters → SLC superfamily of solute carriers → SLC11 family of proton-coupled metal ion transporters

**Overview**: The family of proton-coupled metal ion transporters are responsible for movements of divalent cations, particularly ferrous and manganese ions, across the cell membrane (SLC11A2/DMT1) and across endosomal (SLC11A2/DMT1) or lysosomal/phagosomal membranes (SLC11A1/NRAMP1), dependent on proton transport. Both proteins appear to have 12 TM regions and cytoplasmic N- and C- termini. NRAMP1 is involved in antimicrobial action in macrophages, although its precise mechanism is undefined. Facilitated diffusion of divalent cations into phagosomes may increase intravesicular free radicals to damage the pathogen. Alternatively, export of divalent cations from the phagosome may deprive the pathogen of essential enzyme cofactors. SLC11A2/DMT1 is more widely expressed and appears to assist in divalent cation assimilation from the diet, as well as in phagocytotic cells.

| | | |
|---|---|---|
| Nomenclature | NRAMP1 | DMT1 |
| Systematic nomenclature | SLC11A1 | SLC11A2 |
| HGNC, UniProt | *SLC11A1*, P49279 | *SLC11A2*, P49281 |
| Endogenous substrates | $Mn^{2+}$, $Fe^{2+}$ | $Cd^{2+}$, $Co^{2+}$, $Cu^{2+}$, $Mn^{2+}$, $Fe^{2+}$ |
| Stoichiometry | 1 $H^+$ : 1 $Fe^{2+}$ (out) or 1 $Fe^{2+}$ (in) : 1 $H^+$ (out) | 1 $H^+$ : 1 $Fe^{2+}$ (out) [306] |
| Inhibitors | – | compound 6b ($pIC_{50}$ 7.1) [843] |

**Comments**: Loss-of-function mutations in NRAMP1 are associated with increased susceptibility to microbial infection (OMIM: 607948). Loss-of-function mutations in DMT1 are associated with microcytic anemia (OMIM: 206100).

**Further reading on SLC11 family of proton-coupled metal ion transporters**

Codazzi F *et al.* (2015) Iron entry in neurons and astrocytes: a link with synaptic activity. *Front Mol Neurosci* **8**: 18 [PMID:26089776]

Montalbetti N *et al.* (2013) Mammalian iron transporters: families SLC11 and SLC40. *Mol Aspects Med* **34**: 270-87 [PMID:23506870]

Wessling-Resnick M. (2015) Nramp1 and Other Transporters Involved in Metal Withholding during Infection. *J Biol Chem* **290**: 18984-90 [PMID:26055722]

Zheng W *et al.* (2012) Regulation of brain iron and copper homeostasis by brain barrier systems: implication in neurodegenerative diseases. *Pharmacol Ther* **133**: 177-88 [PMID:22115751]

# SLC12 family of cation-coupled chloride transporters

Transporters → SLC superfamily of solute carriers → SLC12 family of cation-coupled chloride transporters

**Overview**: The SLC12 family of chloride transporters contribute to ion fluxes across a variety of tissues, particularly in the kidney and choroid plexus of the brain. Within this family, further subfamilies are identifiable: NKCC1, NKCC2 and NCC constitute a group of therapeutically-relevant transporters, targets for loop and thiazide diuretics. These 12 TM proteins exhibit cytoplasmic termini and an extended extracellular loop at TM7/8 and are kidney-specific (NKCC2 and NCC) or show a more widespread distribution (NKCC1). A second family, the K-Cl co-transporters are also 12 TM domain proteins with cytoplasmic termini, but with an extended extracellular loop at TM 5/6. CCC6 exhibits structural similarities with the K-Cl co-transporters, while CCC9 is divergent, with 11 TM domains and a cytoplasmic N-terminus and extracellular C-terminus.

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | Kidney-specific Na-K-Cl symporter | Basolateral Na-K-Cl symporter | Na-Cl symporter | K-Cl cotransporter 1 | K-Cl cotransporter 2 |
| Systematic nomenclature | SLC12A1 | SLC12A2 | SLC12A3 | SLC12A4 | SLC12A5 |
| Common abbreviation | NKCC2 | NKCC1 | NCC | KCC1 | KCC2 |
| HGNC, UniProt | *SLC12A1*, Q13621 | *SLC12A2*, P55011 | *SLC12A3*, P55017 | *SLC12A4*, Q9UP95 | *SLC12A5*, Q9H2X9 |
| Stoichiometry | 1 $Na^+$ : 1 $K^+$ : 2 $Cl^-$ (in) | 1 $Na^+$ : 1 $K^+$ : 2 $Cl^-$ (in) | 1 $Na^+$ : 1 $Cl^-$ (in) | 1 $K^+$ : 1 $Cl^-$ (out) | 1 $K^+$ : 1 $Cl^-$ (out) |
| Inhibitors | bumetanide ($pIC_{50}$ 6.5) [322], piretanide ($pIC_{50}$ 6) [322], furosemide ($pIC_{50}$ 5.2) [322] | piretanide ($pIC_{50}$ 5.6) [322], bumetanide ($pIC_{50}$ 5.6) [322], furosemide ($pIC_{50}$ 5.1) [322] | chlorothiazide, cyclothiazide, hydrochlorothiazide, metolazone | DIOA | VU0240551 ($pIC_{50}$ 6.2) [160], DIOA |

| | | | |
|---|---|---|---|
| Nomenclature | K-Cl cotransporter 3 | K-Cl cotransporter 4 | Cation-chloride cotransporter 9 |
| Systematic nomenclature | SLC12A6 | SLC12A7 | SLC12A8 |
| Common abbreviation | KCC3 | KCC4 | CCC9 |
| HGNC, UniProt | *SLC12A6*, Q9UHW9 | *SLC12A7*, Q9Y666 | *SLC12A8*, A0AV02 |
| Substrates | – | – | spermine, L-glutamic acid, spermidine, L-aspartic acid |
| Stoichiometry | 1 $K^+$ : 1 $Cl^-$ (out) | 1 $K^+$ : 1 $Cl^-$ (out) | Unknown |
| Inhibitors | DIOA | DIOA | – |
| Comments | – | – | In mouse studies Slc12a8 has been shown to transport the nicotinamide adenine dinucleotide ($NAD^+$) precursor, nicotinamide mononucleotide (NMN) in to cells, and administration of NMN produces anti-ageing effects *in vivo* [296]. |

**Comments**: DIOA is able to differentiate KCC isoforms from NKCC and NCC transporters, but also inhibits CFTR [366].

**Further reading on SLC12 family of cation-coupled chloride transporters**

Arroyo JP *et al.* (2013) The SLC12 family of electroneutral cation-coupled chloride cotransporters. *Mol Aspects Med* **34**: 288-98 [PMID:23506871]

Bachmann S *et al.* (2017) Regulation of renal Na-(K)-Cl cotransporters by vasopressin. *Pflugers Arch* **469**: 889-897 [PMID:28577072]

Bazúa-Valenti S *et al.* (2016) Physiological role of SLC12 family members in the kidney. *Am J Physiol Renal Physiol* **311**: F131-44 [PMID:27097893]

Huang X *et al.* (2016) Everything we always wanted to know about furosemide but were afraid to ask. *Am J Physiol Renal Physiol* **310**: F958-71 [PMID:26911852]

Kahle KT *et al.* (2015) K-Cl cotransporters, cell volume homeostasis, and neurological disease. *Trends Mol Med* **21**: 513-23 [PMID:26142773]

Martín-Aragón Baudel MA *et al.* (2017) Chloride co-transporters as possible therapeutic targets for stroke. *J Neurochem* **140**: 195-209 [PMID:27861901]

# SLC13 family of sodium-dependent sulphate/carboxylate transporters

Transporters → SLC superfamily of solute carriers → SLC13 family of sodium-dependent sulphate/carboxylate transporters

**Overview**: Within the SLC13 family, two groups of transporters may be differentiated on the basis of the substrates transported: NaS1 and NaS2 convey sulphate, while NaC1-3 transport carboxylates. NaS1 and NaS2 transporters are made up of 13 TM domains, with an intracellular N terminus and are electrogenic with physiological roles in the intestine, kidney and placenta. NaC1, NaC2 and NaC3 are made up of 11 TM domains with an intracellular N terminus and are electrogenic, with physiological roles in the kidney and liver.

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | $Na^+$/sulfate cotransporter | $Na^+$/dicarboxylate cotransporter 1 | $Na^+$/dicarboxylate cotransporter 3 | $Na^+$/sulfate cotransporter | $Na^+$/citrate cotransporter |
| Systematic nomenclature | SLC13A1 | SLC13A2 | SLC13A3 | SLC13A4 | SLC13A5 |
| Common abbreviation | NaS1 | NaC1 | NaC3 | NaS2 | NaC2 |
| HGNC, UniProt | *SLC13A1*, Q9BZW2 | *SLC13A2*, Q13183 | *SLC13A3*, Q8WWT9 | *SLC13A4*, Q9UKG4 | *SLC13A5*, Q86YT5 |
| Endogenous substrates | $SO_4^{2-}$, $S_2O_3^{2-}$, $SeO_4^{2-}$ | citric acid, succinic acid | citric acid, succinic acid | $SO_4^{2-}$ | citric acid, pyruvic acid |
| Stoichiometry | 3 $Na^+$ : 1 $SO_4^{2-}$ (in) | 3 $Na^+$ : 1 dicarboxylate$^{2-}$ (in) | Unknown | 3 $Na^+$ : $SO_4^{2-}$ (in) | Unknown |
| Selective inhibitors | – | – | – | – | BI01383298 ($pIC_{50}$ 7.2) [75] |
| Comments | – | – | – | – | Expressed in hepatocytes where it is involved in the synthesis of sterols and fatty acids. Potential drug target for obesity and diabetes. |

**Further reading on SLC13 family of sodium-dependent sulphate/carboxylate transporters**

Bergeron MJ *et al.* (2013) SLC13 family of $Na^+$-coupled di- and tri-carboxylate/sulfate transporters. *Mol Aspects Med* **34**: 299-312 [PMID:23506872]

Markovich D. (2014) Na+-sulfate cotransporter SLC13A1. *Pflugers Arch* **466**: 131-7 [PMID:24193406]

Pajor AM. (2014) Sodium-coupled dicarboxylate and citrate transporters from the SLC13 family. *Pflugers Arch* **466**: 119-30 [PMID:24114175]

# SLC14 family of facilitative urea transporters

Transporters → SLC superfamily of solute carriers → SLC14 family of facilitative urea transporters

**Overview**: As a product of protein catabolism, urea is moved around the body and through the kidneys for excretion. Although there is experimental evidence for concentrative urea transporters, these have not been defined at the molecular level. The SLC14 family are facilitative transporters, allowing urea movement down its concentration gradient. Multiple splice variants of these transporters have been identified; for UT-A transporters, in particular, there is evidence for cell-specific expression of these variants with functional impact [11, 679]. Topographical modelling suggests that the majority of the variants of SLC14 transporters have 10 TM domains, with a glycosylated extracellular loop at TM5/6, and intracellular C- and N-termini. The UT-A1 splice variant, exceptionally, has 20 TM domains, equivalent to a combination of the UT-A2 and UT-A3 splice variants.

| | | |
|---|---|---|
| Nomenclature | Erythrocyte urea transporter | Kidney urea transporter |
| Systematic nomenclature | SLC14A1 | SLC14A2 |
| Common abbreviation | UT-B | UT-A |
| HGNC, UniProt | *SLC14A1*, Q13336 | *SLC14A2*, Q15849 |
| Substrates | acrylamide [845], acetamide [845], methylurea [845] | – |
| Endogenous substrates | ammonium carbonate [845], urea [845], formamide [845] | urea [483] |
| Stoichiometry | Equilibrative | Equilibrative |
| Inhibitors | compound 1a ($pIC_{50}$ ~8) [466], compound 1a ($pIC_{50}$ 7.6) [466] – Mouse, compound 8ay ($pIC_{50}$ ~5.7) [446] – Rat | compound 8ay ($pIC_{50}$ ~6.8) [446] – Rat |

**Further reading on SLC14 family of facilitative urea transporters**

Esteva-Font C *et al.* (2015) Urea transporter proteins as targets for small-molecule diuretics. *Nat Rev Nephrol* **11**: 113-23 [PMID:25488859]

LeMoine CM *et al.* (2015) Evolution of urea transporters in vertebrates: adaptation to urea's multiple roles and metabolic sources. *J Exp Biol* **218**: 1936-1945 [PMID:26085670]

Pannabecker TL. (2013) Comparative physiology and architecture associated with the mammalian urine concentrating mechanism: role of inner medullary water and urea transport pathways in the rodent medulla. *Am J Physiol Regul Integr Comp Physiol* **304**: R488-503 [PMID:23364530]

Shayakul C *et al.* (2013) The urea transporter family (SLC14): physiological, pathological and structural aspects. *Mol Aspects Med* **34**: 313-22 [PMID:23506873]

Stewart G. (2011) The emerging physiological roles of the SLC14A family of urea transporters. *Br J Pharmacol* **164**: 1780-92 [PMID:21449978]

# SLC15 family of peptide transporters

Transporters → SLC superfamily of solute carriers → SLC15 family of peptide transporters

**Overview**: The Solute Carrier 15 (SLC15) family of peptide transporters, alias $H^+$-coupled oligopeptide cotransporter family, is a group of membrane transporters known for their key role in the cellular uptake of di- and tripeptides (di/tripeptides). Of its members, SLC15A1 (PEPT1) chiefly mediates intestinal absorption of luminal di/tripeptides from overall dietary protein digestion, SLC15A2 (PEPT2) mainly allows renal tubular reuptake of di/tripeptides from ultrafiltration and brain-to-blood efflux of di/tripeptides in the choroid plexus, SLC15A3 (PHT2) and SLC15A4 (PHT1) interact with both di/tripeptides and histidine, e.g. in certain immune cells, and SLC15A5 has unknown physiological function. In addition, the SLC15 family of peptide transporters variably interacts with a very large number of peptidomimetics and peptide-like drugs. It is conceivable, based on the currently acknowledged structural and functional differences, to divide the SLC15 family of peptide transporters into two subfamilies [11].

| | | |
|---|---|---|
| Nomenclature | Peptide transporter 1 | Peptide transporter 2 |
| Systematic nomenclature | SLC15A1 | SLC15A2 |
| Common abbreviation | PEPT1 | PEPT2 |
| HGNC, UniProt | *SLC15A1*, P46059 | *SLC15A2*, Q16348 |
| Substrates | cefadroxil [476, 698, 784], valacyclovir [46, 47, 246, 307, 510], fMet-Leu-Phe [101, 115, 499, 500, 801], muramyl dipeptide [363, 430, 479, 756], D-Ala-Lys-AMCA [276, 295, 423, 691], His-Leu-lopinavir [491], alafosfalin [536], cephalexin [18, 143, 238, 245, 476, 713, 714], valganciclovir [681, 741], mirogabalin [817], $\beta$-Ala-Lys-AMCA [4, 13, 369, 423] | muramyl dipeptide [342, 683], D-Ala-Lys-AMCA [423, 691, 783], $\gamma$-iE-DAP [683, 689], $\beta$-Ala-Lys-AMCA [4, 12, 13, 169, 423, 614, 623, 683, 694, 856, 857], alafosfalin [536], Javamide-I(N-coumaroyltryptophan)/-II(N-caffeoyltryptophan) esters (javamide-I-O-methyl ester and javamide-II-O-methyl ester), acetylated prolyl-glycyl-proline (Ac-PGP; the acetylated form of the collagen-derived matrikine PGP) [610], mirogabalin [817] |
| Endogenous substrates | 5-aminolevulinic acid [22, 63, 179, 357, 406, 434, 535, 635], di/tripeptides including peptides with high intrinsic hydrolysis resistance such as carnosine, anserine and $\gamma$-glutamyl-dipeptides [4, 179, 258, 303, 332, 612, 613, 760, 806] | 5-aminolevulinic acid [179, 357, 806], di/tripeptides including peptides with high intrinsic hydrolysis resistance such as carnosine and anserine [4, 258, 471, 559, 683, 806, 844] |
| Stoichiometry | Transport is electrogenic and involves a variable proton-to-substrate stoichiometry for uptake of neutral and mono- or polyvalently charged peptides, as well as the other substrates tested to date. | Transport is electrogenic and involves a variable proton-to-substrate stoichiometry for uptake of neutral and mono- or polyvalently charged peptides, as well as the other substrates tested to date. |
| Inhibitors | Lys[Z($NO_2$)]-Val (p$K_i$ 5.7) [410, 677], Lys[Z($NO_2$)]-Pro (p$K_i$ 5–5.3) [412], Lys[Z($NO_2$)]-Lys[Z($NO_2$)] (p$K_i$ 4.9) [67], 4-AMBA (p$K_i$ 2.3) [22, 152, 498] | Lys[Z($NO_2$)]-Lys[Z($NO_2$)] (p$K_i$ 8) [67, 719], Lys[Z($NO_2$)]-Val (p$K_i$ 7) [67, 719], Lys[Z($NO_2$)]-Pro (p$K_i$ 6.2) [67, 719], 4-AMBA (p$K_i$ 2.5) [67, 719] |
| Labelled ligands | (3,5)-[$^{19}$F]$_2$-Phe-$\psi$-Ala [32], [$^{11}$C]GlySar [512], [$^{14}$C]GlySar [7, 47, 66, 245, 246, 247, 357, 411, 412, 413, 476, 491, 642, 698, 713, 714, 715], [$^{18}$F]FEPPG [521], [$^3$H]-IPP [269, 270], [$^3$H]-LKP [269, 270], [$^3$H]GlySar [18, 100, 133, 143, 320, 370, 457, 562, 635, 691], [$^3$H]mirogabalin [817], glycyl-[$^{13}C_3$]-sarcosine [763] | (3,5)-[$^{19}$F]$_2$-Phe-$\psi$-Ala [32], Ac-[$^{13}$C,$^{15}$N]PGP [610], [$^{11}$C]GlySar [526], [$^{14}$C]GlySar [240, 245, 246, 247, 343, 357, 411, 413, 465, 476, 642, 713, 715], [$^{18}$F]FEPPG [521], [$^3$H]GlySar [457, 475, 562, 636, 671, 691], [$^3$H]mirogabalin [817] |

| | | |
|---|---|---|
| Comments | Although most di/tripeptides can bind PEPT1, not all of them are substrates. The uptake depends on the structural features (charge, hydrophobicity, size, side chain flexibility, *etc*.) of the di/tripeptide. A variety of dipeptides and drugs interact with PEPT1, including D-Phe-Ala [179, 412], D-Phe-Gln [22], cyclo(L-Hyp-L-Ser) (*i.e*. JBP485) [103, 468], nateglinide [715], glibenclamide [642] and penicillin G (benzylpenicillin) [63]. Among many other molecules, PEPT1 has been shown to interact with L-Dopa-L-Phe [699, 734], D-Phe-Gly-L-Dopa [767], JBP485 prodrugs (*e.g*. JBP485-3-$CH_2$-O-valine, J3V) [376], 5-Aminosalicylic acid (5-ASA) derivatives (*i.e*. Gly-ASA, Glu-ASA, Val-ASA) [516, 832], cinnabar (*i.e*. α-HgS >96%) [800], doxorubicin-tripeptide (*i.e*. doxorubicin-Gly-Gly-Gly) [275], scutellarin methyl ester-4'-dipeptide conjugates (*e.g*. scutellarin methyl ester-4'-Val-homo-Leu) [459], curcumin (CUR)-peptide derivatives (*i.e*. CUR-Phe-Val, CUR-Ile-Val) [841], gemcitabine amino acid ester prodrugs (*i.e*. 5'-L-valyl-gemcitabine, V-Gem) [673, 720], decitabine amino acid ester prodrugs (*e.g*. 5'-*O*-L-valyl-decitabine, L-Val-DAC) [705, 706], didanosine amino acid ester prodrugs (*e.g*. 5'-*O*-L-valyl-didanosine, L-Val-DDI) [821], floxuridine amino acid ester prodrugs (*e.g*. 5'-L-isoleucyl and 5'-L-valyl amino acid ester prodrugs of floxuridine) [435, 436], floxuridine amino acid monoester prodrugs (*e.g*. 5'-*O*-D-valyl-floxuridine) [737], floxuridine dipeptide monoester prodrugs (*e.g*. 5'-L-phenylalanyl-L-tyrosyl-floxuridine, 5'-L-phenylalanyl-L-glycyl-floxuridine, and 5'-L-isoleucyl-L-glycyl-floxuridine) [736], amino acid acyloxy ester prodrugs of guanidine oseltamivir carboxylate (GOC) (*e.g*. GOC-L-Val, the L-valyl acyloxy ethyl prodrug of GOC) [308] and the valyl amino acid prodrug of GOC with the isopropyl-methylene-dioxy linker (*i.e*. GOC-ISP-Val) [353], amino acid acyloxy ester prodrugs of zanamivir (Zan, *e.g*. Zan-L-Val, the L-valyl acycloxy ethyl prodrug of Zan) [310], peramivir-$(CH_2)_2$-L-Val and peramivir-L-Ile [684], thiodipeptide prodrugs of for example, ibuprofen and propofol [227], alanylpyrraline (Ala-Pyrr) and pyrralylalanine (Pyrr-Ala) [257], dipeptide-bound derivatives of $N^6$-(carboxymethyl)lysine (CML) and $N^6$-(1-carboxyethyl)-lysine (CEL) (*i.e*. Ala-CML, CML-Ala, Ala-CEL, CEL-Ala) [329], *Flammulina velutipes* polysaccharide (FVP)-iron (III) complex [FVP-Fe (III) complex] [125], dipeptides of *p*-borono-L-phenylalanine (BPA) and tyrosine (*i.e*. L-Tyr-*p*-L-BPA (Tyr-BPA), *p*-L-BPA-L-tyrosine (BPA-Tyr)) [514] and $Au^{III}$-peptidodithiocarbamato complexes of the type [$Au^{III}Br_2$(dtc-$AA_1$-$AA_2$-OR], in which $AA_1$ = N-methylglycine (Sar), L/D-Pro; $AA_2$ = L/D-Ala, α-aminoisobutyric acid (Aib); R = OtBu, triethylene glycol methyl ether) (*e.g*. dtc-Pro-Aib-OtBu) [80]. In recent years, PEPT1 has been shown to interact with a large variety of specifically targeted (*i.e*. peptide- or amino acid-functionalized) nanoparticles [127, 147, 182, 279, 280, 804], (nano)micelles [377, 772, 799, 810] and nanocomposites [302, 779, 808, 809]. | Although most di/tripeptides can bind PEPT2, not all of them are substrates. The uptake depends on the structural features (charge, hydrophobicity, size, side chain flexibility, *etc*.) of the di/tripeptide. Like PEPT1, PEPT2 interacts with dipeptides and drugs including D-Phe-Ala [179, 718], nateglinide [715], glibenclamide [642], penicillin G (benzylpenicillin) [551], polymyxins (*i.e*. polymyxin B and colistin) [475] and entecavir [807]. PEPT2 has been shown to interact with dipeptides of *p*-borono-L-phenylalanine (BPA) and tyrosine (*i.e*. L-Tyr-*p*-L-BPA (Tyr-BPA), *p*-L-BPA-L-tyrosine (BPA-Tyr)) [514] and with $Au^{III}$-peptidodithiocarbamato complexes of the type [$Au^{III}Br_2$(dtc-$AA_1$-$AA_2$-OR), in which $AA_1$ = *N*-methylglycine (Sar), L/D-Pro; $AA_2$ = L/D-Ala, α-aminoisobutyric acid (Aib); R = OtBu, triethylene glycol methyl ether, *e.g*. dtc-Pro-Aib-OtBu) [80]. |

| | | |
|---|---|---|
| Nomenclature | Peptide transporter 3 | Peptide transporter 4 |
| Systematic nomenclature | SLC15A3 | SLC15A4 |
| Common abbreviation | PHT2 | PHT1 |
| HGNC, UniProt | *SLC15A3*, Q8IY34 | *SLC15A4*, Q8N697 |
| Substrates | MDP-rhodamine [529], muramyl dipeptide [529, 777], glycyl-sarcosine [778], Tri-DAP [777], cefadroxil [778], valacyclovir [778] | muramyl dipeptide [529, 672], MDP-rhodamine [342, 529], Tri-DAP [444, 640, 672], C12-iE-DAP [444], His-Leu-lopinavir [491], glycyl-sarcosine [62, 343, 672, 691], valacyclovir [62] |
| Endogenous substrates | L-histidine [634, 778], carnosine [559, 634], glycyl-glycyl-glycine [778] | L-histidine [62, 415, 491, 775, 820], carnosine [62, 559, 820], glycyl-glycyl-glycine [559] |

| | | |
|---|---|---|
| Stoichiometry | PHT2 has not been analyzed systematically with respect to driving force, mode of transport, and substrate specificity. The pH dependence observed for transport of histidine [634] and the model peptides used, *i.e.*, carnosine [634] and histidyl-leucine [634], suggest a similar mode of operation as PEPT1 and PEPT2 proteins. | PHT1 has not been analyzed systematically with respect to driving force, mode of transport, and substrate specificity. The pH dependence observed for transport of histidine [62, 415, 491, 775, 820] and the model peptide used, *i.e.*, carnosine [62, 820], suggest a similar mode of operation as PEPT1 and PEPT2 proteins. |
| Labelled ligands | [$^{14}$C]histidine [634] | [$^{14}$C]histidine (Binding) [775, 776, 820], [$^{3}$H]histidine [62, 491, 691, 775] |
| Comments | Other PHT2 ligands include $d_3$-L-histidine [778] and [$^{3}$H]carnosine [634]. | Other PHT1 ligands include $d_3$-L-histidine [672], [$^{3}$H]carnosine [62, 820], [$^{14}$C]GlySar [343], [$^{3}$H]GlySar [62, 691] and [$^{3}$H]valacyclovir [62]. Recently, PHT1 has been shown to interact with specifically targeted (*i.e.* peptide-functionalized) nanoparticles [805]. |

**Comments**: The members of the SLC15 family of peptide transporters are particularly promiscuous in the transport of di/tripeptides, and D-amino acid containing peptides are also transported. While SLC15A3 and SLC15A4 transport histidine, none of them transport tetrapeptides. In addition, many molecules, among which beta-lactam antibacterials, angiotensin-converting enzyme inhibitors and sartans, variably interact with the SLC15 family transporters. Known substrates include cefadroxil, valacyclovir, 5-aminolevulinic acid, L-Dopa prodrugs, gemcitabine prodrugs, floxuridine prodrugs, Maillard reaction products, JBP485 and JBP485 prodrugs, zanamivir prodrugs, oseltamivir prodrugs, doxorubicin prodrugs, polymyxins, didanosine prodrugs, decitabine prodrugs, peramivir prodrugs, ibuprofen and propofol thiodipeptide prodrugs, curcumin-peptide derivatives, 5-aminosalicylic acid derivatives, cinnabar, dipeptide conjugates of scutellarin, *Flammulina velutipes* polysaccharide-iron (III) complex, *p*-borono-L-phenylalanine-containing dipeptides and $Au^{III}$-peptidodithiocarbamato complexes. Known substrates also include mirogabalin, javamide-I/-II esters, acetylated di/tripeptides, LY2140023, paclitaxel small molecule prodrugs, JBP923 enantiomers, fluorescein-labeled dipeptides and peptide-bound derivatives of carboxymethyllysine. Notably, PEPT1 interacts with a variety of specifically PEPT1-targeted (*via* peptide- or amino acid-functionalization) nanoparticles, (nano)micelles and nanocomposites. Frequently used pharmaceutical excipients such as Tween 20, Tween 80, Solutol HS 15 and Cremophor EL strongly inhibit cellular uptake of Gly-Sar by SLC15A1 and/or SLC15A2 [562].

There is evidence to suggest the existence of a fifth member of this transporter family, *SLC15A5* (A6NIM6; ENSG00000188991), but to date there is no established biological function or reported pharmacology for this protein [674].

**Further reading on SLC15 family of peptide transporters**

Anderson CM *et al.* (2010) Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* **25**: 364-77 [PMID:21186281]
Gyimesi G *et al.* (2023) Transporter-Mediated Drug Delivery. *Molecules* **28**: [PMID:36770817]
Parker JL *et al.* (2021) Cryo-EM structure of PepT2 reveals structural basis for proton-coupled peptide and prodrug transport in mammals. *Sci Adv* **7**: [PMID:34433568]
Smith DE *et al.* (2013) Proton-coupled oligopeptide transporter family SLC15: physiological, pharmacological and pathological implications. *Mol Aspects Med* **34**: 323-36 [PMID:23506874]
Toyama-Sorimachi N *et al.* (2021) Lysosomal amino acid transporters as key players in inflammatory diseases. *Int Immunol* **33**: 853-858 [PMID:34508637]

# SLC16 family of monocarboxylate transporters

Transporters → SLC superfamily of solute carriers → SLC16 family of monocarboxylate transporters

**Overview**: Members of the SLC16 family may be divided into subfamilies on the basis of substrate selectivities, particularly lactate (*e.g.* L-lactic acid), pyruvic acid and ketone bodies, as well as aromatic amino acids. Topology modelling suggests 12 TM domains, with intracellular termini and an extended loop at TM 6/7.

The proton-coupled monocarboxylate transporters (monocarboxylate transporters 1, 4, 2 and 3) allow transport of the products of cellular metabolism, principally lactate (*e.g.* L-lactic acid) and pyruvic acid.

| Nomenclature | Monocarboxylate transporter 1 | Monocarboxylate transporter 2 | Monocarboxylate transporter 3 | Monocarboxylate transporter 4 | Monocarboxylate transporter 6 | Monocarboxylate transporter 8 | Monocarboxylate transporter 10 |
|---|---|---|---|---|---|---|---|
| Systematic nomenclature | SLC16A1 | SLC16A7 | SLC16A8 | SLC16A3 | SLC16A5 | SLC16A2 | SLC16A10 |
| Common abbreviation | MCT1 | MCT2 | MCT3 | MCT4 | MCT6 | MCT8 | TAT1 |
| HGNC, UniProt | *SLC16A1*, P53985 | *SLC16A7*, O60669 | *SLC16A8*, O95907 | *SLC16A3*, O15427 | *SLC16A5*, O15375 | *SLC16A2*, P36021 | *SLC16A10*, Q8TF71 |
| Substrates | $\gamma$-hydroxybutyric acid [774] | – | – | – | – | – | – |
| Endogenous substrates | $\beta$-D-hydroxybutyric acid, L-lactic acid, pyruvic acid | L-lactic acid, pyruvic acid | L-lactic acid | L-lactic acid, pyruvic acid | – | triiodothyronine [235], $T_4$ [235] | L-tryptophan, L-phenylalanine, levodopa, L-tyrosine |
| Stoichiometry | 1 $H^+$ : 1 monocarboxylate$^-$ (out) | 1 $H^+$ : 1 monocarboxylate$^-$ (out) | 1 $H^+$ : 1 monocarboxylate$^-$ (out) | 1 $H^+$ : 1 monocarboxylate$^-$ (out) | Unknown | Unknown | Unknown |
| Inhibitors | BAY-8002 ($pIC_{50}$ 9) [592], AZD3965 ($pK_i$ 8.5) [146], compound 30 (Compound 30 is a channel blocker.) ($pK_i$ 8.3) [305], BAY-8002 ($pK_i$ 8.3) [592] | BAY-8002 ($pIC_{50}$ 8.3) [592], 7ACC2 ($pIC_{50}$ 8) [181], AZD3965 ($pK_i$ 7.7) [146] | – | compound 18n ($pIC_{50}$ 9) [327] | – | – | – |
| Comments | – | – | – | – | MCT6 has been reported to transport bumetanide, but not short chain fatty acids [523]. | – | – |

**Comments**: MCT1 and MCT2, but not MCT3 and MCT4, are inhibited by CHC, which also inhibits members of the mitochondrial transporter family, SLC25.

MCT5-MCT7, MCT9 and MCT11-14 are regarded as orphan transporters.

### Further reading on SLC16 family of monocarboxylate transporters

Bernal J *et al.* (2015) Thyroid hormone transporters-functions and clinical implications. *Nat Rev Endocrinol* **11**: 406-417 [PMID:25942657]

Bosshart PD *et al.* (2021) SLC16 Family: From Atomic Structure to Human Disease. *Trends Biochem Sci* **46**: 28-40 [PMID:32828650]

Felmlee MA *et al.* (2020) Monocarboxylate Transporters (SLC16): Function, Regulation, and Role in Health and Disease. *Pharmacol Rev* **72**: 466-485 [PMID:32144120]

Halestrap AP. (2013) The SLC16 gene family - structure, role and regulation in health and disease. *Mol Aspects Med* **34**: 337-49 [PMID:23506875]

Jones RS *et al.* (2016) Monocarboxylate Transporters: Therapeutic Targets and Prognostic Factors in Disease. *Clin Pharmacol Ther* **100**: 454-463 [PMID:27351344]

# SLC17 phosphate and organic anion transporter family

Transporters → SLC superfamily of solute carriers → SLC17 phosphate and organic anion transporter family

**Overview**: The SLC17 family are sometimes referred to as Type I sodium-phosphate co-transporters, alongside Type II (SLC34 family) and Type III (SLC20 family) transporters. Within the SLC17 family, however, further subgroups of organic anion transporters may be defined, allowing the accumulation of sialic acid in the endoplasmic reticulum and glutamate (*e.g.* L-glutamic acid) or nucleotides in synaptic and secretory vesicles. Topology modelling suggests 12 TM domains.

# Type I sodium-phosphate co-transporters

Transporters → SLC superfamily of solute carriers → SLC17 phosphate and organic anion transporter family → Type I sodium-phosphate co-transporters

**Overview**: Type I sodium-phosphate co-transporters are expressed in the kidney and intestine.

| | | | | |
|---|---|---|---|---|
| Nomenclature | Sodium/phosphate cotransporter 1 | Sodium/phosphate cotransporter 3 | Sodium/phosphate cotransporter 4 | Sodium/phosphate cotransporter homolog |
| Systematic nomenclature | SLC17A1 | SLC17A2 | SLC17A3 | SLC17A4 |
| Common abbreviation | NPT1 | NPT3 | NPT4 | – |
| HGNC, UniProt | *SLC17A1*, Q14916 | *SLC17A2*, O00624 | *SLC17A3*, O00476 | *SLC17A4*, Q9Y2C5 |
| Substrates | probenecid [99], penicillin G [99], organic acids [351], $Cl^-$ [351], uric acid [351], phosphate [351] | – | – | – |
| Stoichiometry | Unknown | Unknown | Unknown | Unknown |

# Sialic acid transporter

Transporters → SLC superfamily of solute carriers → SLC17 phosphate and organic anion transporter family → Sialic acid transporter

**Overview**: The sialic acid transporter is expressed on both lysosomes and synaptic vesicles, where it appears to allow export of sialic acid and accumulation of acidic amino acids, respectively [515], driven by proton gradients. In lysosomes, degradation of glycoproteins generates amino acids and sugar residues, which are metabolized further following export from the lysosome.

| | |
|---|---|
| Nomenclature | Sialin |
| Systematic nomenclature | SLC17A5 |
| Common abbreviation | AST |
| HGNC, UniProt | *SLC17A5*, Q9NRA2 |
| Endogenous substrates | L-glutamic acid (in) [515], L-aspartic acid [515], L-lactic acid, gluconate (out), sialic acid, glucuronic acid |
| Stoichiometry | 1 $H^+$ : 1 sialic acid (out) |

**Comments**: Loss-of-function mutations in sialin are associated with Salla disease (OMIM: 604369), an autosomal recessive neurodegenerative disorder associated with sialic acid storage disease [758].

# Vesicular glutamate transporters (VGLUTs)

Transporters → SLC superfamily of solute carriers → SLC17 phosphate and organic anion transporter family → Vesicular glutamate transporters (VGLUTs)

**Overview**: Vesicular glutamate transporters (VGLUTs) allow accumulation of glutamate into synaptic vesicles, as well as secretory vesicles in endocrine tissues. The roles of VGLUTs in kidney and liver are unclear. These transporters appear to utilize the proton gradient and also express a chloride conductance [57].

| | | | |
|---|---|---|---|
| Nomenclature | Vesicular glutamate transporter 1 | Vesicular glutamate transporter 2 | Vesicular glutamate transporter 3 |
| Systematic nomenclature | SLC17A7 | SLC17A6 | SLC17A8 |
| Common abbreviation | VGLUT1 | VGLUT2 | VGLUT3 |
| HGNC, UniProt | *SLC17A7*, Q9P2U7 | *SLC17A6*, Q9P2U8 | *SLC17A8*, Q8NDX2 |
| Endogenous substrates | L-glutamic acid > D-glutamic acid | L-glutamic acid > D-glutamic acid | L-glutamic acid > D-glutamic acid |
| Stoichiometry | Unknown | Unknown | Unknown |

**Comments**: Endogenous ketoacids produced during fasting have been proposed to regulate VGLUT function through blocking chloride ion-mediated allosteric enhancement of transporter function [381].

# Vesicular nucleotide transporter

Transporters → SLC superfamily of solute carriers → SLC17 phosphate and organic anion transporter family → Vesicular nucleotide transporter

**Overview**: The vesicular nucleotide transporter is the most recent member of the SLC17 family to have an assigned function. Uptake of ATP was independent of pH, but dependent on chloride ions and membrane potential [641].

| | |
|---|---|
| Nomenclature | Vesicular nucleotide transporter |
| Systematic nomenclature | SLC17A9 |
| Common abbreviation | VNUT |
| HGNC, UniProt | *SLC17A9*, Q9BYT1 |
| Endogenous substrates | ATP [641], guanosine-5'-triphosphate [641], guanosine 5'-diphosphate [641] |
| Stoichiometry | Unknown |
| Selective inhibitors | clodronic acid ($pIC_{50}$ 7.8) [395] |

**Comments**: VGLUTs and VNUT can be inhibited by DIDS and evans blue dye.

**Further reading on SLC17 phosphate and organic anion transporter family**

Moriyama Y *et al*. (2017) Vesicular nucleotide transporter (VNUT): appearance of an actress on the stage of purinergic signaling. *Purinergic Signal* **13**: 387-404 [PMID:28616712]

Omote H *et al*. (2016) Structure, Function, and Drug Interactions of Neurotransmitter Transporters in the Postgenomic Era. *Annu Rev Pharmacol Toxicol* **56**: 385-402 [PMID:26514205]

Reimer RJ. (2013) SLC17: a functionally diverse family of organic anion transporters. *Mol Aspects Med* **34**: 350-9 [PMID:23506876]

Takamori S. (2016) Vesicular glutamate transporters as anion channels? *Pflugers Arch* **468**: 513-8 [PMID:26577586]

# SLC18 family of vesicular amine transporters

Transporters → SLC superfamily of solute carriers → SLC18 family of vesicular amine transporters

**Overview**: The vesicular amine transporters (VATs) are putative 12 TM domain proteins that function to transport singly positively charged amine neurotransmitters and hormones from the cytoplasm and concentrate them within secretory vesicles. They function as amine/proton antiporters driven by secondary active transport utilizing the proton gradient established by a multi-subunit vacuolar ATPase that acidifies secretory vesicles (reviewed by [193]). The vesicular acetylcholine transporter (VAChT; [204]) localizes to cholinergic neurons, but non-neuronal expression has also been claimed [646]. Vesicular monoamine transporter 1 (VMAT1, [202]) is mainly expressed in peripheral neuroendocrine cells, but most likely not in the CNS, whereas VMAT2 [203] distributes between both central and peripheral sympathetic monoaminergic neurones [194]. The vescular polyamine transporter (VPAT) is highly expressed in the lungs and placenta, with moderate expression in brain and testis, and with low expression in heart and skeletal muscle [334]. VPAT mediates vesicular accumulation of polyamines in mast cells [695].

| | | | |
|---|---|---|---|
| Nomenclature | Vesicular monoamine transporter 1 | Vesicular monoamine transporter 2 | Vesicular acetylcholine transporter |
| Systematic nomenclature | SLC18A1 | SLC18A2 | SLC18A3 |
| Common abbreviation | VMAT1 | VMAT2 | VAChT |
| HGNC, UniProt | *SLC18A1*, P54219 | *SLC18A2*, Q05940 | *SLC18A3*, Q16572 |
| Substrates | β-phenylethylamine ($K_i$ $3.4 \times 10^{-5}$M) [203], $MPP^+$ ($K_i$ $6.9 \times 10^{-5}$ M) [203], MDMA ($K_i$ $1.9 \times 10^{-5}$M) [203], fenfluramine ($K_i$ $3.1 \times 10^{-6}$M) [203], dexamfetamine ($K_i$ $4.7 \times 10^{-5}$M) [203] | β-phenylethylamine ($K_i$ $3.7 \times 10^{-6}$M) [203], fenfluramine ($K_i$ $5.1 \times 10^{-6}$ M) [203], MDMA ($K_i$ $6.9 \times 10^{-6}$M) [203], dexamfetamine ($K_i$ $2.1 \times 10^{-6}$ M) [203], $MPP^+$ ($K_i$ $8.9 \times 10^{-6}$M) [203] | $TPP^+$ [84], ethidium [84], N-methyl-pyridinium-2-aldoxime [84], N-(4'-pentanonyl)-4-(4"-dimethylamino-styryl)pyridinium [84] |
| Endogenous substrates | (-)-adrenaline ($K_i$ $5.5 \times 10^{-6}$M) [203], (-)-noradrenaline ($K_i$ $1.3 \times 10^{-5}$M) [203], dopamine ($K_i$ $3.8 \times 10^{-6}$M) [203], histamine ($K_i$ $4.6 \times 10^{-3}$M) [203], 5-hydroxytryptamine ($K_i$ $1.4 \times 10^{-6}$M) [203] | 5-hydroxytryptamine ($K_i$ $9 \times 10^{-7}$M) [203], (-)-adrenaline ($K_i$ $1.9 \times 10^{-6}$ M) [203], (-)-noradrenaline ($K_i$ $3.4 \times 10^{-6}$M) [203], dopamine ($K_i$ $1.4 \times 10^{-6}$M) [203], histamine ($K_i$ $1.4 \times 10^{-4}$M) [203] | acetylcholine ($K_i$ $7.9 \times 10^{-4}$M) [85, 401], choline ($K_i$ $5 \times 10^{-3}$M) [85, 401] |
| Stoichiometry | 1 amine (in): $2H^+$ (out) | 1 amine (in): $2H^+$ (out) | 1 amine (in): $2H^+$ (out) |
| Inhibitors | reserpine ($pK_i$ 7.5) [203], ketanserin ($pK_i$ 5.8) [203], tetrabenazine ($pK_i$ 4.7) [203] | reserpine ($pK_i$ 7.9) [203], tetrabenazine ($pK_i$ 7) [203], ketanserin ($pK_i$ 6.3) [203] | aminobenzovesamicol ($pK_i$ 10.9) [192], vesamicol ($pK_i$ 8.7) [192] |
| Labelled ligands | – | [$^3$H]TBZOH (Inhibitor) ($pK_d$ 8.2) [754], [$^{125}$I]iodovinyl-TBZ (Inhibitor) ($pK_d$ 8.1) [431], [$^{11}$C]DTBZ (Inhibitor), [$^{125}$I]7-azido-8-iodoketanserine (Inhibitor) [665] | [$^3$H]vesamicol ($pK_d$ 8.4) [754], [$^{123}$I]iodobenzovesamicol |

**Comments**: $pK_i$ values for endogenous and synthetic substrate inhibitors of human VMAT1 and VMAT2 are for inhibition of [$^3$H]5-HT uptake in transfected and permeabilised CV-1 cells as detailed by [203]. In addition to the monoamines listed in the table, the trace amines tyramine and β-phenylethylamine are probable substrates for VMAT2 [194]. Probes listed in the table are those currently employed; additional agents have been synthesized (*e.g.* [854]).

### Further reading on SLC18 family of vesicular amine transporters

German CL *et al.* (2015) Regulation of the Dopamine and Vesicular Monoamine Transporters: Pharmacological Targets and Implications for Disease. *Pharmacol Rev* **67**: 1005-24 [PMID:26408528]

Lohr KM *et al.* (2017) Membrane transporters as mediators of synaptic dopamine dynamics: implications for disease. *Eur J Neurosci* **45**: 20-33 [PMID:27520881]

Omote H *et al.* (2016) Structure, Function, and Drug Interactions of Neurotransmitter Transporters in the Postgenomic Era. *Annu Rev Pharmacol Toxicol* **56**: 385-402 [PMID:26514205]

Sitte HH *et al.* (2015) Amphetamines, new psychoactive drugs and the monoamine transporter cycle. *Trends Pharmacol Sci* **36**: 41-50 [PMID:25542076]

Wimalasena K. (2011) Vesicular monoamine transporters: structure-function, pharmacology, and medicinal chemistry. *Med Res Rev* **31**: 483-519 [PMID:20135628]

# SLC19 family of vitamin transporters

Transporters → SLC superfamily of solute carriers → SLC19 family of vitamin transporters

**Overview**: The B vitamins folic acid and thiamine are transported across the cell membrane, particularly in the intestine, kidneys and placenta, using pH differences as driving forces. Topological modelling suggests the transporters have 12 TM domains.

| | | | |
|---|---|---|---|
| Nomenclature | Reduced folate transporter 1 | Thiamine transporter 1 | Thiamine transporter 2 |
| Systematic nomenclature | SLC19A1 | SLC19A2 | SLC19A3 |
| Common abbreviation | FOLT | ThTr1 | ThTr2 |
| HGNC, UniProt | *SLC19A1*, P41440 | *SLC19A2*, O60779 | *SLC19A3*, Q9BZV2 |
| Substrates | folinic acid, methotrexate, folic acid [586], $N^5$-formyltetrahydrofolate | – | – |
| Endogenous substrates | tetrahydrofolic acid [586], $N^5$-methylfolate [586], thiamine monophosphate [846], Other tetrahydrofolate-cofactors, Organic phosphates; in particular, adenine nucleotides | thiamine | thiamine |
| Stoichiometry | Folate (in) : organic phosphate (out), precise stoichiometry unknown | A facilitative carrier not known to be coupled to an inorganic or organic ion gradient | A facilitative carrier not known to be coupled to an inorganic or organic ion gradient |
| Inhibitors | compound 9 ($pK_i$ 6.6) [618], methotrexate ($pK_i$ 5.3) [618] | – | – |
| Labelled ligands | [$^3$H]folic acid [36], [$^3$H]methotrexate [36] | [$^3$H]thiamine [188] | [$^3$H]thiamine [599] |

**Comments**: Loss-of-function mutations in ThTr1 underlie thiamine-responsive megaloblastic anemia syndrome [168].

### Further reading on SLC19 family of vitamin transporters

Matherly LH *et al.* (2014) The major facilitative folate transporters solute carrier 19A1 and solute carrier 46A1: biology and role in antifolate chemotherapy of cancer. *Drug Metab Dispos* **42**: 632-49 [PMID:24396145]

Zhao R *et al.* (2013) Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors. *Mol Aspects Med* **34**: 373-85 [PMID:23506878]

# SLC20 family of sodium-dependent phosphate transporters

Transporters → SLC superfamily of solute carriers → SLC20 family of sodium-dependent phosphate transporters

**Overview**: The SLC20 family is looked upon not only as ion transporters, but also as retroviral receptors. As ion transporters, they are sometimes referred to as Type III sodium-phosphate co-transporters, alongside Type I (SLC17 family) and Type II (SLC34 family). PiTs are cell-surface transporters, composed of ten TM domains with extracellular C- and N-termini. PiT1 is a focus for dietary phosphate and vitamin D regulation of parathyroid hormone secretion from the parathyroid gland. PiT2 appears to be involved in intestinal absorption of dietary phosphate.

| | | |
|---|---|---|
| Nomenclature | Sodium-dependent phosphate transporter 1 | Sodium-dependent phosphate transporter 2 |
| Systematic nomenclature | SLC20A1 | SLC20A2 |
| Common abbreviation | PiT1 | PiT2 |
| HGNC, UniProt | *SLC20A1*, Q8WUM9 | *SLC20A2*, Q08357 |
| Substrates | $AsO_4^{3-}$ [600], phosphate [600] | phosphate [600] |
| Stoichiometry | >1 $Na^+$ : 1 $HPO_4^{2-}$ (in) | >1 $Na^+$ : 1 $HPO_4^{2-}$ (in) |

**Further reading on SLC20 family of sodium-dependent phosphate transporters**

Biber J *et al.* (2013) Phosphate transporters and their function. *Annu Rev Physiol* **75**: 535-50 [PMID:23398154]

Forster IC *et al.* (2013) Phosphate transporters of the SLC20 and SLC34 families. *Mol Aspects Med* **34**: 386-95 [PMID:23506879]

Shobeiri N *et al.* (2014) Phosphate: an old bone molecule but new cardiovascular risk factor. *Br J Clin Pharmacol* **77**: 39-54 [PMID:23506202]

# SLC22 family of organic cation and anion transporters

Transporters → SLC superfamily of solute carriers → SLC22 family of organic cation and anion transporters

**Overview**: The SLC22 family of transporters is mostly composed of non-selective transporters, which are expressed highly in liver, kidney and intestine, playing a major role in drug disposition. The family may be divided into three subfamilies based on the nature of the substrate transported: organic cations (OCTs), organic anions (OATs) and organic zwiterrion/cations (OCTN). Membrane topology is predicted to contain 12 TM domains with intracellular termini, and an extended extracellular loop at TM 1/2.

# Organic cation transporters (OCT)

Transporters → SLC superfamily of solute carriers → SLC22 family of organic cation and anion transporters → Organic cation transporters (OCT)

**Overview**: Organic cation transporters (OCT) are electrogenic, $Na^+$-independent and reversible.

| | | | |
|---|---|---|---|
| Nomenclature | Organic cation transporter 1 | Organic cation transporter 2 | Organic cation transporter 3 |
| Systematic nomenclature | SLC22A1 | SLC22A2 | SLC22A3 |
| Common abbreviation | OCT1 | OCT2 | OCT3 |
| HGNC, UniProt | *SLC22A1*, O15245 | *SLC22A2*, O15244 | *SLC22A3*, O75751 |
| Substrates | tetraethylammonium, desipramine, $MPP^+$, aciclovir, metformin [664] | tubocurarine [278], tetraethylammonium [278], pancuronium [278], $MPP^+$ [278], metformin [418], cisplatin [418] | quinidine, tetraethylammonium, $MPP^+$, metformin [418] |
| Endogenous substrates | 5-hydroxytryptamine, $PGE_2$, $PGF_2\alpha$, choline | dopamine [297], histamine [297], $PGE_2$ [405] | 5-hydroxytryptamine [853], (-)-noradrenaline [853], dopamine [853] |
| Stoichiometry | Unknown | Unknown | Unknown |
| Inhibitors | clonidine ($pK_i$ 6.3) [842] | decynium 22 ($pK_i$ 7) [278] | disprocynium24 ($pK_i$ 7.8) [298] |

**Comments**: Corticosterone and quinine are able to inhibit all three organic cation transporters.

**Further reading on Organic cation transporters (OCT)**


Koepsell H. (2020) Organic Cation Transporters in Health and Disease. *Pharmacol Rev* **72**: 253-319 [PMID:31852803]

Lozano E *et al.* (2013) Role of the plasma membrane transporter of organic cations OCT1 and its genetic variants in modern liver pharmacology. *Biomed Res Int* **2013**: 692071 [PMID:23984399]

Pelis RM *et al.* (2014) SLC22, SLC44, and SLC47 transporters–organic anion and cation transporters: molecular and cellular properties. *Curr Top Membr* **73**: 233-61 [PMID:24745985]

Samodelov SL *et al.* (2020) Organic Cation Transporters in Human Physiology, Pharmacology, and Toxicology. *Int J Mol Sci* **21**: [PMID:33114309]

Yee SW *et al.* (2021) Emerging Roles of the Human Solute Carrier 22 Family. *Drug Metab Dispos* **50**: 1193-210 [PMID:34921098]

Yin J *et al.* (2016) Renal drug transporters and their significance in drug-drug interactions. *Acta Pharm Sin B* **6**: 363-373 [PMID:27709005]

# Organic zwitterions/cation transporters (OCTN)

Transporters → SLC superfamily of solute carriers → SLC22 family of organic cation and anion transporters → Organic zwitterions/cation transporters (OCTN)

**Overview**: Organic zwitterions/cation transporters (OCTN) function as organic cation uniporters, organic cation/proton exchangers or sodium/L-carnitine co-transporters.

| | | | |
|---|---|---|---|
| Nomenclature | Organic cation/carnitine transporter 1 | Organic cation/carnitine transporter 2 | Carnitine transporter 2 |
| Systematic nomenclature | SLC22A4 | SLC22A5 | SLC22A16 |
| Common abbreviation | OCTN1 | OCTN2 | CT2 |
| HGNC, UniProt | *SLC22A4*, Q9H015 | *SLC22A5*, O76082 | *SLC22A16*, Q86VW1 |
| Substrates | mepyramine, tetraethylammonium, verapamil, $MPP^+$ | mepyramine, tetraethylammonium, verapamil, $MPP^+$ | – |
| Endogenous substrates | L-carnitine | acetyl-L-carnitine, L-carnitine | L-carnitine |
| Stoichiometry | Unknown | Unknown | Unknown |

**Comments**: Mutations in the *SLC22A5* gene lead to primary carnitine deficiency [470].

**Further reading on Organic zwitterions/cation transporters (OCTN)**

Matthaei J *et al.* (2016) OCT1 mediates hepatic uptake of sumatriptan and loss-of-function OCT1 polymorphisms affect sumatriptan pharmacokinetics. *Clin Pharmacol Ther* **99**: 633-41 [PMID:26659468]

Tamai I. (2013) Pharmacological and pathophysiological roles of carnitine/organic cation transporters (OCTNs: SLC22A4, SLC22A5 and Slc22a21). *Biopharm Drug Dispos* **34**: 29-44 [PMID:22952014]

Yin J *et al.* (2016) Renal drug transporters and their significance in drug-drug interactions. *Acta Pharm Sin B* **6**: 363-373 [PMID:27709005]

# Organic anion transporters (OATs)

Transporters → SLC superfamily of solute carriers → SLC22 family of organic cation and anion transporters → Organic anion transporters (OATs)

**Overview**: Organic anion transporters (OATs) are non-selective transporters prominent in the kidney, placenta and blood-brain barrier.

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | Organic anion transporter 1 | Organic anion transporter 2 | Organic anion transporter 3 | Organic anion transporter 4 | Organic anion transporter 7 |
| Systematic nomenclature | SLC22A6 | SLC22A7 | SLC22A8 | SLC22A11 | SLC22A9 |
| Common abbreviation | OAT1 | OAT2 | OAT3 | – | OAT4 |
| HGNC, UniProt | *SLC22A6*, Q4U2R8 | *SLC22A7*, Q9Y694 | *SLC22A8*, Q8TCC7 | *SLC22A11*, Q9NSA0 | *SLC22A9*, Q8IVM8 |

| | | | | | |
|---|---|---|---|---|---|
| Substrates | non-steroidal anti-inflammatory drugs, aminohippuric acid | non-steroidal anti-inflammatory drugs, $PGE_2$, aminohippuric acid | cimetidine [432], ochratoxin A [432], estrone-3-sulphate [432], aminohippuric acid [432], uric acid [542] | dehydroepiandrosterone sulphate [110], estrone-3-sulphate [110], ochratoxin A [110], uric acid [542] | – |
| Stoichiometry | Unknown | Unknown | Unknown | Unknown | Unknown |
| Inhibitors | probenecid (Inhibition of urate transport by human SCL22A6.) ($pIC_{50}$ 4.9) [349] | – | – | – | – |

**Further reading on Organic anion transporters (OATs)**


Burckhardt G *et al*. (2011) In vitro and in vivo evidence of the importance of organic anion transporters (OATs) in drug therapy. *Handb Exp Pharmacol* 29-104 [PMID:21103968]

Koepsell H. (2013) The SLC22 family with transporters of organic cations, anions and zwitterions. *Mol Aspects Med* **34**: 413-35 [PMID:23506881]

Nigam SK. (2018) The SLC22 Transporter Family: A Paradigm for the Impact of Drug Transporters on Metabolic Pathways, Signaling, and Disease. *Annu Rev Pharmacol Toxicol* **58**: 663-687 [PMID:29309257]

Shen H *et al*. (2017) Organic Anion Transporter 2: An Enigmatic Human Solute Carrier. *Drug Metab Dispos* **45**: 228-236 [PMID:27872146]

Yee SW *et al*. (2021) Emerging Roles of the Human Solute Carrier 22 Family. *Drug Metab Dispos* **50**: 1193-210 [PMID:34921098]

Yin J *et al*. (2016) Renal drug transporters and their significance in drug-drug interactions. *Acta Pharm Sin B* **6**: 363-373 [PMID:27709005]


# Urate transporter

Transporters → SLC superfamily of solute carriers → SLC22 family of organic cation and anion transporters → Urate transporter

**Overview**: URAT1, a member of the OAT (organic anion transporter) family, is an anion-exchanging uptake transporter localized to the apical (brush border) membrane of renal proximal tubular cells. It is an anion exchanger that selectively reabsorbs uric acid from the proximal tubule in exchange for monovalent anions such as lactate, nicotinoate, acetoacetate, and hydroxybutyrate [201].

| | |
|---|---|
| Nomenclature | Urate anion exchanger 1 |
| Systematic nomenclature | SLC22A12 |
| Common abbreviation | URAT1 |
| HGNC, UniProt | *SLC22A12*, Q96S37 |
| Endogenous substrates | orotic acid [201], uric acid [201] |
| Stoichiometry | Unknown |
| Selective inhibitors | dotinurad ($pIC_{50}$ 6.4) [703], sufinpyrazone ($pIC_{50}$ 4) [831], lesinurad [98] |
| Comments | URAT1 is expressed in the proximal tubule of the kidney and regulates uric acid excretion from the body. Inhibitors of this transporter, such as losartan, find clinical utility in managing hyperuricemia in patients with gout [98, 316]. |

**Further reading on Urate transporter**

Nigam SK *et al.* (2018) The systems biology of uric acid transporters: the role of remote sensing and signaling. *Curr Opin Nephrol Hypertens* **27**: 305-313 [PMID:29847376]

# Atypical SLC22B subfamily

Transporters → SLC superfamily of solute carriers → SLC22 family of organic cation and anion transporters → Atypical SLC22B subfamily

**Overview**: This family of transporters has previously been classified as part of the atypical major facilitator superfamily (MSF) protein superfamily [11, 568, 572, 573, 601]. The atypical SLCs share sequence similarities and phylogenetic ancestry with other SLCs, and they have historically been classified in to subfamilies (also referred to as atypical MFS transporter families (AMTF1-15)) based on phylogenetic, sequence and structural analyses [572].

| | |
|---|---|
| Nomenclature | synaptic vesicle glycoprotein 2A |
| Systematic nomenclature | SLC22B1 |
| HGNC, UniProt | *SV2A*, Q7L0J3 |
| Substrates | Galactose [484] |
| Inhibitors | brivaracetam ($pIC_{50}$ 7) [398] – Rat, levetiracetam ($pK_i$ 5.8) [547] – Rat |

**Comments**: There are three human synaptic vesicle glycoprotein 2 family members, SV2A, SV2B and SV2C. They have transmembrane transporter activity and can be classified in to the SLC superfamily of solute carriers in subfamily SLC22, as SCL22B1, B2 and B3 respectively. SV2A (SCL22B1) has been identified as the brain binding-site for the antiepileptic drugs levetiracetam [408, 472] and brivaracetam [540].

**Further reading on Atypical SLC22B subfamily**

Löscher W *et al.* (2016) Synaptic Vesicle Glycoprotein 2A Ligands in the Treatment of Epilepsy and Beyond. *CNS Drugs* **30**: 1055-1077 [PMID:27752944]

Mendoza-Torreblanca JG *et al.* (2013) Synaptic vesicle protein 2A: basic facts and role in synaptic function. *Eur J Neurosci* **38**: 3529-39 [PMID:24102679]

**Further reading on SLC22 family of organic cation and anion transporters**

Burckhardt G. (2012) Drug transport by Organic Anion Transporters (OATs). *Pharmacol Ther* **136**: 106-30 [PMID:22841915]

Hillgren KM *et al.* (2013) Emerging transporters of clinical importance: an update from the International Transporter Consortium. *Clin Pharmacol Ther* **94**: 52-63 [PMID:23588305]

Koepsell H. (2013) The SLC22 family with transporters of organic cations, anions and zwitterions. *Mol Aspects Med* **34**: 413-35 [PMID:23506881]

Nigam SK. (2018) The SLC22 Transporter Family: A Paradigm for the Impact of Drug Transporters on Metabolic Pathways, Signaling, and Disease. *Annu Rev Pharmacol Toxicol* **58**: 663-687 [PMID:29309257]

Yee SW *et al.* (2021) **Emerging Roles of the Human Solute Carrier 22 Family**. *Drug Metab Dispos* **50**: 1193-210 [PMID:34921098]

Zamek-Gliszczynski MJ *et al.* (2018) Transporters in Drug Development: 2018 ITC Recommendations for Transporters of Emerging Clinical Importance. *Clin Pharmacol Ther* **104**: 890-899 [PMID:30091177]

# SLC23 family of ascorbic acid transporters

Transporters → SLC superfamily of solute carriers → SLC23 family of ascorbic acid transporters

**Overview**: Predicted to be 12 TM segment proteins, members of this family transport the reduced form of ascorbic acid (while the oxidized form may be handled by members of the SLC2 family (GLUT1/SLC2A1, GLUT3/SLC2A3 and GLUT4/SLC2A4). Phloretin is considered a non-selective inhibitor of these transporters, with an affinity in the micromolar range [11].

| | | | |
|---|---|---|---|
| Nomenclature | Sodium-dependent vitamin C transporter 1 | Sodium-dependent vitamin C transporter 2 | Sodium-dependent vitamin C transporter 3 |
| Systematic nomenclature | SLC23A1 | SLC23A2 | SLC23A3 |
| Common abbreviation | SVCT1 | SVCT2 | SVCT3 |
| HGNC, UniProt | *SLC23A1*, Q9UHI7 | *SLC23A2*, Q9UGH3 | *SLC23A3*, Q6PIS1 |
| Endogenous substrates | L-ascorbic acid > D-ascorbic acid > dehydroascorbic acid [735] | L-ascorbic acid > D-ascorbic acid > dehydroascorbic acid [735] | – |
| Stoichiometry | 2 $Na^+$: 1 ascorbic acid (in) [735] | 2 $Na^+$: 1 ascorbic acid (in) [735] | – |
| Inhibitors | phloretin ($pK_i$ 4.2) [735] | – | – |
| Labelled ligands | [$^{14}$C]ascorbic acid (Binding) [480] | [$^{14}$C]ascorbic acid | – |
| Comments | – | – | SLC23A3 does not transport ascorbic acid and remains an orphan transporter. |

| | |
|---|---|
| Nomenclature | Sodium-dependent nucleobase transporter |
| Systematic nomenclature | SLC23A4 |
| Common abbreviation | SNBT1 |
| HGNC, UniProt | *SLC23A4P*, – |
| Substrates | 5-fluorouracil [815] |
| Endogenous substrates | uracil > thymine > guanine, hypoxanthine > xanthine, uridine [815] |
| Stoichiometry | 1 $Na^+$ : 1 uracil (in) [815] |
| Comments | SLC23A4/SNBT1 is found in rodents and non-human primates, but the sequence is truncated in the human genome and named as a pseudogene, SLC23A4P |

**Further reading on SLC23 family of ascorbic acid transporters**

Bürzle M *et al.* (2013) The sodium-dependent ascorbic acid transporter family SLC23. *Mol Aspects Med* **34**: 436-54 [PMID:23506882]

May JM. (2011) The SLC23 family of ascorbate transporters: ensuring that you get and keep your daily dose of vitamin C. *Br J Pharmacol* **164**: 1793-801 [PMID:21418192]

# SLC24 family of sodium/potassium/calcium exchangers

Transporters → SLC superfamily of solute carriers → SLC24 family of sodium/potassium/calcium exchangers

**Overview**: The sodium/potassium/calcium exchange family of transporters utilize the extracellular sodium gradient to drive calcium and potassium co-transport out of the cell. As is the case for NCX transporters (SLC8A family), NKCX transporters are thought to be bidirectional, with the possibility of calcium influx following depolarization of the plasma membrane. Topological modeling suggests the presence of 10 TM domains, with a large intracellular loop between the fifth and sixth TM regions.

| | | |
|---|---|---|
| Nomenclature | Sodium/potassium/calcium exchanger 1 | Sodium/potassium/calcium exchanger 6 |
| Systematic nomenclature | SLC24A1 | SLC24A6 |
| Common abbreviation | NKCX1 | NKCX6 |
| HGNC, UniProt | *SLC24A1*, O60721 | *SLC8B1*, Q6J4K2 |
| Stoichiometry | $4Na^+$:($1Ca^{2+}$ + $1K^+$) | – |
| Inhibitors | – | CGP-37157 ($pIC_{50}$ 5.8) [494] |

**Comments**: NKCX6 has been proposed to be the sole member of a CAX $Na^+/Ca^{2+}$ exchanger family, which may be the mitochondrial transporter responsible for calcium accumulation from the cytosol [652].

**Further reading on SLC24 family of sodium/potassium/calcium exchangers**

Schnetkamp PP. (2013) The SLC24 gene family of $Na^+/Ca^{2+}$-$K^+$ exchangers: from sight and smell to memory consolidation and skin pigmentation. *Mol Aspects Med* **34**: 455-64 [PMID:23506883]

Schnetkamp PP *et al.* (2014) The SLC24 family of $K^+$-dependent $Na^+$-$Ca^{2+}$ exchangers: structure-function relationships. *Curr Top Membr* **73**: 263-87 [PMID:24745986]

Sekler I. (2015) Standing of giants shoulders the story of the mitochondrial Na(+)Ca(2+) exchanger. *Biochem Biophys Res Commun* **460**: 50-2 [PMID:25998733]

# SLC25 family of mitochondrial transporters

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters

**Overview**: Mitochondrial carriers are nuclear-encoded proteins, which translocate solutes across the inner mitochondrial membrane. Mitochondrial carriers are functional as monomers and have six TM alpha-helices and the termini in the mitochondrial intermembrane space.

# Mitochondrial di- and tri-carboxylic acid transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters → Mitochondrial di- and tri-carboxylic acid transporter subfamily

**Overview**: Mitochondrial di- and tri-carboxylic acid transporters are grouped on the basis of commonality of substrates and include the citrate transporter which facilitates citric acid export from the mitochondria to allow the generation of oxalacetic acid and acetyl CoA through the action of ATP:citrate lyase.

| | | | | |
|---|---|---|---|---|
| Nomenclature | Mitochondrial citrate transporter | Mitochondrial dicarboxylate transporter | Mitochondrial oxoglutarate carrier | Mitochondrial oxodicarboxylate carrier |
| Systematic nomenclature | SLC25A1 | SLC25A10 | SLC25A11 | SLC25A21 |
| Common abbreviation | CIC | DIC | OGC | ODC |
| HGNC, UniProt | *SLC25A1*, P53007 | *SLC25A10*, Q9UBX3 | *SLC25A11*, Q02978 | *SLC25A21*, Q9BQT8 |
| Substrates | citric acid, phosphoenolpyruvic acid, malic acid | succinic acid, malic acid, $S_2O_3^{2-}$, $SO_4^{2-}$, phosphate | α-ketoglutaric acid, malic acid | α-ketoglutaric acid, α-oxoadipic acid |
| Stoichiometry | $Malate^{2-}$ (in) : H-$citrate^{2-}$ (out) | $PO_3^{4-}$ (in) : $malate^{2-}$ (out) | $Malate^{2-}$ (in) : $oxoglutarate^{2-}$ (out) | Oxoadipate (in) : oxoglutarate (out) |
| Inhibitors | 1,2,3-benzenetricarboxylic acid | – | – | – |

# Mitochondrial amino acid transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters → Mitochondrial amino acid transporter subfamily

**Overview**: Mitochondrial amino acid transporters can be subdivided on the basis of their substrates. Mitochondrial ornithine transporters play a role in the urea cycle by exchanging cytosolic ornithine (L-ornithine and D-ornithine) for mitochondrial citrulline (L-citrulline and D-citrulline) in equimolar amounts. Further members of the family include transporters of S-adenosylmethionine and carnitine.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nomenclature | AGC1 | AGC2 | Mitochondrial glutamate carrier 2 | Mitochondrial glutamate carrier 1 | Mitochondrial ornithine transporter 2 | Mitochondrial ornithine transporter 1 | Carnitine/acylcarnitine carrier |
| Systematic nomenclature | SLC25A12 | SLC25A13 | SLC25A18 | SLC25A22 | SLC25A2 | SLC25A15 | SLC25A20 |
| Common abbreviation | – | – | GC2 | GC1 | ORC2 | ORC1 | CAC |
| HGNC, UniProt | *SLC25A12*, O75746 | *SLC25A13*, Q9UJS0 | *SLC25A18*, Q9H1K4 | *SLC25A22*, Q9H936 | *SLC25A2*, Q9BXI2 | *SLC25A15*, Q9Y619 | *SLC25A20*, O43772 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Substrates | L-glutamic acid, L-aspartic acid, 2-amino-3-sulfinopropanoic acid | L-glutamic acid, L-aspartic acid, 2-amino-3-sulfinopropanoic acid | L-glutamic acid | L-glutamic acid | L-arginine [223], L-citrulline [223], L-lysine [223], L-ornithine [223], L-histidine [223], D-histidine [223], D-arginine [223], D-lysine [223], D-ornithine [223], D-citrulline [223] | L-arginine [223], L-citrulline [223], L-lysine [223], L-ornithine [223] | – |
| Stoichiometry | Aspartate : glutamate $H^+$ (bidirectional) | Aspartate : glutamate $H^+$ (bidirectional) | Glutamate : $H^+$ (bidirectional) | Glutamate : $H^+$ (bidirectional) | 1 Ornithine (in) :1 citrulline : 1 $H^+$ (out) | 1 Ornithine (in) :1 citrulline : 1 $H^+$ (out) | – |
| Comments | – | – | – | – | – | – | Exchanges cytosolic acylcarnitine for mitochondrial carnitine |

**Comments**: Both ornithine transporters are inhibited by the polyamine spermine [224]. Loss-of-function mutations in these genes are associated with hyperornithinemia-hyperammonemia-homocitrullinuria.

**Further reading on Mitochondrial amino acid transporter subfamily**

Hewton KG *et al.* (2021) Transporters at the Interface between Cytosolic and Mitochondrial Amino Acid Metabolism. *Metabolites* **11**: [PMID:33669382]

# Mitochondrial phosphate transporters

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters → Mitochondrial phosphate transporters

**Overview**: Mitochondrial phosphate transporters allow the import of inorganic phosphate for ATP production.

| | |
|---|---|
| Nomenclature | Mitochondrial phosphate carrier |
| Systematic nomenclature | SLC25A3 |
| Common abbreviation | PHC |
| HGNC, UniProt | *SLC25A3*, Q00325 |
| Stoichiometry | $PO_3^{4-}$ (in) : $OH^-$ (out) or $PO_3^{4-}$ : $H^+$ (in) |

# Mitochondrial nucleotide transporter subfamily

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters → Mitochondrial nucleotide transporter subfamily

**Overview**: Mitochondrial nucleotide transporters, defined by structural similarlities, include the adenine nucleotide translocator family (SLC25A4, SLC25A5, SLC25A6 and SLC25A31), which under conditions of aerobic metabolism, allow coupling between mitochondrial oxidative phosphorylation and cytosolic energy consumption by exchanging cytosolic ADP for mitochondrial ATP. Further members of the mitochondrial nucleotide transporter subfamily convey diverse substrates including CoA, although not all members have had substrates identified.

| Nomenclature | Mitochondrial adenine nucleotide translocator 1 | Mitochondrial adenine nucleotide translocator 2 | Mitochondrial adenine nucleotide translocator 3 | Mitochondrial adenine nucleotide translocator 4 | Graves disease carrier | Peroxisomal membrane protein |
|---|---|---|---|---|---|---|
| Systematic nomenclature | SLC25A4 | SLC25A5 | SLC25A6 | SLC25A31 | SLC25A16 | SLC25A17 |
| Common abbreviation | ANT1 | ANT2 | ANT3 | ANT4 | GDC | PMP34 |
| HGNC, UniProt | *SLC25A4*, P12235 | *SLC25A5*, P05141 | *SLC25A6*, P12236 | *SLC25A31*, Q9H0C2 | *SLC25A16*, P16260 | *SLC25A17*, O43808 |
| Substrates | – | – | – | – | CoA and congeners | ADP, ATP, adenosine 5'-monophosphate |
| Stoichiometry | $ADP^{3-}$ (in) : $ATP^{4-}$ (out) | $ADP^{3-}$ (in) : $ATP^{4-}$ (out) | $ADP^{3-}$ (in) : $ATP^{4-}$ (out) | $ADP^{3-}$ (in) : $ATP^{4-}$ (out) | CoA (in) | ATP (in) |
| Inhibitors | bongkrek acid, carboxyatractyloside | – | – | – | – | – |

| Nomenclature | Deoxynucleotide carrier 1 | S-Adenosylmethionine carrier | Mitochondrial phosphate carrier 1 | Mitochondrial phosphate carrier 2 | Mitochondrial phosphate carrier 3 |
|---|---|---|---|---|---|
| Systematic nomenclature | SLC25A19 | SLC25A26 | SLC25A24 | SLC25A23 | SLC25A25 |
| Common abbreviation | DNC | SAMC1 | APC1 | APC2 | APC3 |
| HGNC, UniProt | *SLC25A19*, Q9HC21 | *SLC25A26*, Q70HW3 | *SLC25A24*, Q6NUK1 | *SLC25A23*, Q9BV35 | *SLC25A25*, Q6KCM7 |
| Substrates | Deoxynucleotide Triphosphates (dNTPs), Deoxynucleotide Diphosphates (dNDPs), Nucleotide Diphosphates (NDPs), Dideoxynucleotide Triphosphates (ddNTPs) | S-adenosyl methionine | – | – | – |
| Stoichiometry | dNDP (in) : ATP (out) | – | – | – | – |

### Further reading on Mitochondrial nucleotide transporter subfamily

Ruprecht JJ *et al.* (2019) Structural changes in the transport cycle of the mitochondrial ADP/ATP carrier. *Curr Opin Struct Biol* **57**: 135-144 [PMID:31039524]

Ruprecht JJ *et al.* (2021) Structural Mechanism of Transport of Mitochondrial Carriers. *Annu Rev Biochem* **90**: 535-558 [PMID:33556281]

# Mitochondrial uncoupling proteins

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters → Mitochondrial uncoupling proteins

**Overview**: Mitochondrial uncoupling proteins allow dissipation of the mitochondrial proton gradient associated with thermogenesis and regulation of radical formation.

| | | | | | | |
|---|---|---|---|---|---|---|
| Nomenclature | Uncoupling protein 1 | Uncoupling protein 2 | Uncoupling protein 3 | Uncoupling protein 4 | Uncoupling protein 5 | KMCP1 |
| Systematic nomenclature | SLC25A7 | SLC25A8 | SLC25A9 | SLC25A27 | SLC25A14 | SLC25A30 |
| Common abbreviation | UCP1 | UCP2 | UCP3 | UCP4 | UCP5 | – |
| HGNC, UniProt | *UCP1*, P25874 | *UCP2*, P55851 | *UCP3*, P55916 | *SLC25A27*, O95847 | *SLC25A14*, O95258 | *SLC25A30*, Q5SVS4 |
| Stoichiometry | $H^+$ (in) | $H^+$ (in) | $H^+$ (in) | $H^+$ (in) | $H^+$ (in) | – |

# Miscellaneous SLC25 mitochondrial transporters

Transporters → SLC superfamily of solute carriers → SLC25 family of mitochondrial transporters → Miscellaneous SLC25 mitochondrial transporters

**Overview**: Many of the transporters identified below have yet to be assigned functions and are currently regarded as orphans.

Information on members of this family may be found in the online database.

**Further reading on SLC25 family of mitochondrial transporters**


Baffy G. (2017) Mitochondrial uncoupling in cancer cells: Liabilities and opportunities. *Biochim Biophys Acta* **1858**: 655-664 [PMID:28088333]

Crichton PG *et al.* (2017) The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism. *Biochimie* **134**: 35-50 [PMID:28057583]

Dolce V *et al.* (2014) Mitochondrial tricarboxylate and dicarboxylate-tricarboxylate carriers: from animals to plants. *IUBMB Life* **66**: 462-71 [PMID:25045044]

Klingenberg M. (2017) UCP1 - A sophisticated energy valve. *Biochimie* **134**: 19-27 [PMID:27794497]

Kunji ERS *et al.* (2020) The SLC25 Carrier Family: Important Transport Proteins in Mitochondrial Physiology and Pathology. *Physiology (Bethesda)* **35**: 302-327 [PMID:32783608]

Lytovchenko O *et al.* (2017) Expression and putative role of mitochondrial transport proteins in cancer. *Biochim Biophys Acta Bioenerg* **1858**: 641-654 [PMID:28342810]

Nicholls DG. (2017) The hunt for the molecular mechanism of brown fat thermogenesis. *Biochimie* **134**: 9-18 [PMID:27621145]

Palmieri F *et al.* (2022) Mitochondrial transport and metabolism of the vitamin B-derived cofactors thiamine pyrophosphate, coenzyme A, FAD and $NAD^+$ , and related diseases: A review. *IUBMB Life* **74**: 592-617 [PMID:35304818]

Palmieri F *et al.* (2020) Diseases Caused by Mutations in Mitochondrial Carrier Genes *SLC25*: A Review. *Biomolecules* **10**: [PMID:32340404]

Ruprecht JJ *et al.* (2020) The SLC25 Mitochondrial Carrier Family: Structure and Mechanism. *Trends Biochem Sci* **45**: 244-258 [PMID:31787485]

# SLC26 family of anion exchangers

Transporters → SLC superfamily of solute carriers → SLC26 family of anion exchangers

**Overview**: Along with the SLC4 family, the SLC26 family acts to allow movement of monovalent and divalent anions across cell membranes. The predicted topology is of 10-14 TM domains with intracellular C- and N-termini, probably existing as dimers. Within the family, subgroups may be identified on the basis of functional differences, which appear to function as anion exchangers and anion channels (SLC26A7 and SLC26A9).

# Selective sulphate transporters

Transporters → SLC superfamily of solute carriers → SLC26 family of anion exchangers → Selective sulphate transporters

| | | |
|---|---|---|
| Nomenclature | Sat-1 | DTDST |
| Systematic nomenclature | SLC26A1 | SLC26A2 |
| HGNC, UniProt | *SLC26A1*, Q9H2B4 | *SLC26A2*, P50443 |
| Substrates | oxalate, $SO_4^{2-}$ | $SO_4^{2-}$ |
| Stoichiometry | $SO_4^{2-}$ (in) : anion (out) | 1 $SO_4^{2-}$ (in) : 2 $Cl^-$ (out) |

# Chloride/bicarbonate exchangers

Transporters → SLC superfamily of solute carriers → SLC26 family of anion exchangers → Chloride/bicarbonate exchangers

| | | | |
|---|---|---|---|
| Nomenclature | DRA | Pendrin | PAT-1 |
| Systematic nomenclature | SLC26A3 | SLC26A4 | SLC26A6 |
| HGNC, UniProt | *SLC26A3*, P40879 | *SLC26A4*, O43511 | *SLC26A6*, Q9BXS9 |
| Substrates | $Cl^-$ | $Cl^-$, formate, $OH^-$, $I^-$, $HCO_3^-$ | $Cl^-$, oxalate, formate, $OH^-$, $SO_4^{2-}$, $I^-$, $HCO_3^-$ |
| Stoichiometry | 2 $Cl^-$ (in) : 1 $HCO_3^-$ (out) or 2 $Cl^-$ (in) : 1 $OH^-$ (out) | Unknown | 1 $SO_4^{2-}$ (in) : 2 $HCO_3^-$ (out) or 1 $Cl^-$ (in) : 2 $HCO_3^-$ (out) |

# Anion channels

Transporters → SLC superfamily of solute carriers → SLC26 family of anion exchangers → Anion channels

| | | |
|---|---|---|
| Nomenclature | SLC26A7 | SLC26A9 |
| HGNC, UniProt | *SLC26A7*, Q8TE54 | *SLC26A9*, Q7LBE3 |
| Substrates | $NO_3^-$ ≫ $Cl^-$ = $Br^-$ = $I^-$ > $SO_4^{2-}$ = L-glutamic acid | $I^-$ > $Br^-$ > $NO_3^-$ > $Cl^-$ > L-glutamic acid |
| Functional Characteristics | Voltage- and time-independent current, linear I-V relationship [403] | Voltage- and time-independent current, linear I-V relationship [180] |
| Comments | – | SLC26A9 has been suggested to operate in two additional modes as a $Cl^-$-$HCO_3^-$ exchanger and as a $Na^+$-anion cotransporter [112]. |

# Other SLC26 anion exchangers

Transporters → SLC superfamily of solute carriers → SLC26 family of anion exchangers → Other SLC26 anion exchangers

| | |
|---|---|
| Nomenclature | Prestin |
| Systematic nomenclature | SLC26A5 |
| HGNC, UniProt | *SLC26A5*, P58743 |
| Substrates | $Cl^-$ [511], $HCO_3^-$ [511] |
| Stoichiometry | Unknown |
| Comments | Prestin has been suggested to function as a molecular motor, rather than a transporter |

**Further reading on SLC26 family of anion exchangers**

Alper SL *et al.* (2013) The SLC26 gene family of anion transporters and channels. *Mol Aspects Med* **34**: 494-515 [PMID:23506885]

Kato A *et al.* (2011) Regulation of electroneutral NaCl absorption by the small intestine. *Annu Rev Physiol* **73**: 261-81 [PMID:21054167]

Nofziger C *et al.* (2011) Pendrin function in airway epithelia. *Cell Physiol Biochem* **28**: 571-8 [PMID:22116372]

Soleimani M. (2013) SLC26 Cl-/HCO3- exchangers in the kidney: roles in health and disease. *Kidney Int* **84**: 657-66 [PMID:23636174]

# SLC27 family of fatty acid transporters

Transporters → SLC superfamily of solute carriers → SLC27 family of fatty acid transporters

**Overview**: Fatty acid transporter proteins (FATPs) are a family (SLC27) of six transporters (FATP1-6). They have at least one, and possibly six [455, 643], transmembrane segments, and are predicted on the basis of structural similarities to form dimers. SLC27 members have several structural domains: integral membrane associated domain, peripheral membrane associated domain, FATP signature, intracellular AMP binding motif, dimerization domain, lipocalin motif, and an ER localization domain (identified in FATP4 only) [210, 507, 560]. These transporters are unusual in that they appear to express intrinsic very long-chain acyl-CoA synthetase (EC 6.2.1.- , EC 6.2.1.7) enzyme activity. Within the cell, these transporters may associate with plasma and peroxisomal membranes. FATP1-4 and -6 transport long- and very long-chain fatty acids, while FATP5 transports long-chain fatty acids as well as bile acids [11, 506, 643].

| Nomenclature | Fatty acid transport protein 1 | Fatty acid transport protein 2 | Fatty acid transport protein 3 | Fatty acid transport protein 4 | Fatty acid transport protein 5 | Fatty acid transport protein 6 |
|---|---|---|---|---|---|---|
| Systematic nomenclature | SLC27A1 | SLC27A2 | SLC27A3 | SLC27A4 | SLC27A5 | SLC27A6 |
| Common abbreviation | FATP1 | FATP2 | FATP3 | FATP4 | FATP5 | FATP6 |
| HGNC, UniProt | *SLC27A1*, Q6PCB7 | *SLC27A2*, O14975 | *SLC27A3*, Q5K4L6 | SLC27A4, Q6P1M0 | *SLC27A5*, Q9Y2P5 | SLC27A6, Q9Y2P4 |
| Endogenous substrates | arachidonic acid > palmitic acid > oleic acid > butyric acid [643] palmitic acid > oleic acid > γ-linolenic acid > octanoic acid [266] | – | – | palmitic acid > oleic acid > butyric acid, γ-linolenic acid > arachidonic acid [675] palmitic acid , oleic acid > γ-linolenic acid > octanoic acid [266] | – | palmitic acid > oleic acid > γ-linolenic acid > octanoic acid [266 |
| Inhibitors | – | – | – | compound 1l ($pIC_{50}$ 7.1) [70] | – | – |
| Comments | – | – | – | FATP4 is genetically linked to restrictive dermopathy | – | – |

**Comments**: Although the stoichiometry of fatty acid transport is unclear, it has been proposed to be facilitated by the coupling of fatty acid transport to conjugation with coenzyme A to form fatty acyl CoA esters. Small molecule inhibitors of FATP2 [456, 639] and FATP4 [70, 852], as well as bile acid inhibitors of FATP5 [852], have been described; analysis of the mechanism of action of some of these inhibitors suggests that transport may be selectively inhibited without altering enzymatic activity of the FATP.

C1-BODIPY-C12 accumulation has been used as a non-selective index of fatty acid transporter activity.

FATP2 has two variants: Variant 1 encodes the full-length protein, while Variant 2 encodes a shorter isoform missing an internal protein segment. FATP6 also has two variants: Variant 2 encodes the same protein as Variant 1 but has an additional segment in the 5′ UTR.

### Further reading on SLC27 family of fatty acid transporters

Anderson CM *et al.* (2013) SLC27 fatty acid transport proteins. *Mol Aspects Med* **34**: 516-28 [PMID:23506886]

Dourlen P *et al.* (2015) Fatty acid transport proteins in disease: New insights from invertebrate models. *Prog Lipid Res* **60**: 30-40 [PMID:26416577]

Schwenk RW *et al.* (2010) Fatty acid transport across the cell membrane: regulation by fatty acid transporters. *Prostaglandins Leukot Essent Fatty Acids* **82**: 149-54 [PMID:20206486]

# SLC28 and SLC29 families of nucleoside transporters

Transporters → SLC superfamily of solute carriers → SLC28 and SLC29 families of nucleoside transporters

**Overview**: Nucleoside transporters are divided into two families, the sodium-dependent, concentrative solute carrier family 28 (SLC28) and the equilibrative, solute carrier family 29 (SLC29). The endogenous substrates are typically nucleosides, although some family members can also transport nucleobases and organic cations [11].

# SLC28 family

Transporters → SLC superfamily of solute carriers → SLC28 and SLC29 families of nucleoside transporters → SLC28 family

**Overview**: SLC28 family membersappear to have 13 TM segments with cytoplasmic N-termini and extracellular C-termini, and function as concentrative nucleoside transporters.

| | | | |
|---|---|---|---|
| Nomenclature | Sodium/nucleoside cotransporter 1 | Sodium/nucleoside cotransporter 2 | Solute carrier family 28 member 3 |
| Systematic nomenclature | SLC28A1 | SLC28A2 | SLC28A3 |
| Common abbreviation | CNT1 | CNT2 | CNT3 |
| HGNC, UniProt | *SLC28A1*, O00337 | *SLC28A2*, O43868 | *SLC28A3*, Q9HAS3 |
| Substrates | gemcitabine [129], zidovudine, zalcitabine, ribavirin [130] | formycin B [438], cladribine [564], vidarabine, didanosine, fludarabine [438] | zalcitabine, 5-fluorouridine, zebularine, formycin B, gemcitabine, cladribine, floxuridine, didanosine, zidovudine |
| Endogenous substrates | adenosine, uridine, thymidine, cytidine | adenosine, inosine, guanosine, thymidine | adenosine, inosine, uridine, guanosine, thymidine, cytidine |
| Stoichiometry | 1 $Na^+$ : 1 nucleoside (in) | 1 $Na^+$ : 1 nucleoside (in) | 2 $Na^+/H^+$ |
| Inhibitors | – | – | compound 16 ($pK_i$ 5.5) [311] |
| Comments | – | – | CNT3 forms cyclic homotrimers [678]. Genetic variants of *SLC28A3* are associated with increased risk of anthracycline-induced cardiomyopathy [676]. |

**Further reading on SLC28 family**

Johnson ZL *et al.* (2014) Structural basis of nucleoside and nucleoside drug selectivity by concentrative nucleoside transporters. *Elife* **3**: e03604 [PMID:25082345]
Pastor-Anglada M *et al.* (2008) SLC28 genes and concentrative nucleoside transporter (CNT) proteins. *Xenobiotica* **38**: 972-94 [PMID:18668436]
Pastor-Anglada M *et al.* (2018) Who Is Who in Adenosine Transport. *Front Pharmacol* **9**: 627 [PMID:29962948]
Pastor-Anglada M *et al.* (2015) Nucleoside transporter proteins as biomarkers of drug responsiveness and drug targets. *Front Pharmacol* **6**: 13 [PMID:25713533]
Young JD *et al.* (2013) The human concentrative and equilibrative nucleoside transporter families, SLC28 and SLC29. *Mol Aspects Med* **34**: 529-47 [PMID:23506887]

# SLC29 family

Transporters → SLC superfamily of solute carriers → SLC28 and SLC29 families of nucleoside transporters → SLC29 family

**Overview**: SLC29 family members are composed of 11 TM segments with cytoplasmic N-termini and extracellular C-termini. ENT1, ENT2 and ENT4 are primarily cell-surface transporters, while ENT3 is intracellular, possibly lysosomal [45]]. ENT2 isoforms may also play a role in the nucleolar transport of nucleosides [288]. ENT1-3 are described as broad-spectrum equilibrative nucleoside transporters. ENT4 is primarily a polyspecific organic cation transporter at neutral pH [337], but transports adenosine and analogues such as 2-chloroadenosine, with affinities similar to other members of the SLC29 family, at acidic pH [701].

| | | |
|---|---|---|
| Nomenclature | Equilibrative nucleoside transporter 1 | Equilibrative nucleoside transporter 2 |
| Systematic nomenclature | SLC29A1 | SLC29A2 |
| Common abbreviation | ENT1 | ENT2 |
| HGNC, UniProt | *SLC29A1*, Q99808 | *SLC29A2*, Q14542 |
| Endogenous substrates in order of increasing Km: | adenosine < inosine < uridine < guanosine < cytidine < hypoxanthine < adenine < thymine | – |
| Substrates | formycin B, tubercidin, gemcitabine, cladribine, floxuridine, pentostatin, vidarabine, 2-chloroadenosine, cytarabine, zalcitabine, didanosine, ribavirin [130], abacavir [109], atenolol [508] | formycin B, tubercidin, gemcitabine, cladribine, vidarabine, zidovudine, cytarabine, 2-chloroadenosine |
| Endogenous substrates | adenosine [823], inosine [823], guanosine [823], thymidine [823], cytidine [823], adenine [823], uridine [823], hypoxanthine [823], thymine [823] | adenosine, inosine, hypoxanthine, uridine, guanosine, thymidine, guanine, thymine, cytosine |
| Stoichiometry | Equilibrative | Equilibrative |
| Inhibitors | nitrobenzylmercaptopurine ribonucleoside ($pK_i$ 9.7), draflazine ($pK_i$ 9.6) [317], KF24345 ($pK_i$ 9.4) [318], NBTGR ($pK_i$ 9.3), dilazep ($pK_i$ 9), dipyridamole ($pK_i$ 8.8) [318], ticagrelor ($pK_i$ 7.3) [33] | – |
| Labelled ligands | [$^3$H]nitrobenzylmercaptopurine ribonucleoside ($pK_d$ 9.3) | – |
| Comments | SLC29A1 (ENT1) has 100-1000-fold lower affinity for nucleobases as compared with nucleosides [823]. The affinities of draflazine, dilazep, KF24345 and dipyridamole at SLC29A1 transporters are species dependent, exhibiting lower affinity at rat transporters than at human transporters [318, 685]. Dilazep and nitrobenzylmercaptopurine ribonucleoside have distinct but overlapping binding domains in the SLC29A1 crystal structure [797]. The loss of SLC29A1 activity in SLC29A1-null mice has been associated with a hypermineralization disorder similar to human diffuse idiopathic skeletal hyperostosis [781]. Lack of SLC29A1 also results in the Augustine-null blood type [150]. SLC29A1 forms homodimers and heterodimers (with SLC29A2) [289]. | – |

| | | |
|---|---|---|
| Nomenclature | Equilibrative nucleoside transporter 3 | Plasma membrane monoamine transporter |
| Systematic nomenclature | SLC29A3 | SLC29A4 |
| Common abbreviation | ENT3 | PMAT |
| HGNC, UniProt | *SLC29A3*, Q9BZD2 | *SLC29A4*, Q7RTT9 |
| Substrates | didanosine [45], cordycepin [45], zebularine [45], tubercidin [45], cladribine [45], fludarabine [45], zalcitabine [45], floxuridine [45], zidovudine [45] | tetraethylammonium [200, 770], $MPP^+$ [200, 770], metformin [851], atenolol [508] |
| Endogenous substrates | adenosine [45], inosine [45], uridine [45], guanosine [45], thymidine [45], adenine [45] | dopamine [200, 770], 5-hydroxytryptamine [200, 770], histamine [200, 770], tyramine [200, 770], adenosine [850] |
| Stoichiometry | Equilibrative | Equilibrative |
| Inhibitors | – | decynium 22 ($pK_i$ 7) [200, 770], rhodamine123 ($pK_i$ 6) [200, 770], dipyridamole ($pK_i$ 5.9) [766], verapamil ($pK_i$ 4.7) [200, 770], fluoxetine ($pK_i$ 4.6) [200, 770], quinidine ($pK_i$ 4.6) [200, 770], quinine ($pK_i$ 4.6) [200, 770], desipramine ($pK_i$ 4.5) [200, 770], cimetidine ($pK_i$ <3.3) [200, 770] |
| Comments | Defects in *SLC29A3* have been implicated in histiocytosis-lymphadenopathy plus syndrome (OMIM:602782) and lysosomal storage diseases [341, 391]. | Uptake of substrates by PMAT is pH dependent, with greater uptake observed at acidic extracellular pH [51, 851]. |

**Further reading on SLC29 family**

Boswell-Casteel RC *et al.* (2017) Equilibrative nucleoside transporters-A review. *Nucleosides Nucleotides Nucleic Acids* **36**: 7-30 [PMID:27759477]
Pastor-Anglada M *et al.* (2018) Who Is Who in Adenosine Transport. *Front Pharmacol* **9**: 627 [PMID:29962948]
Wang J. (2016) The plasma membrane monoamine transporter (PMAT): Structure, function, and role in organic cation disposition. *Clin Pharmacol Ther* **100**: 489-499 [PMID:27506881]

**Further reading on SLC28 and SLC29 families of nucleoside transporters**

Boswell-Casteel RC *et al.* (2017) Equilibrative nucleoside transporters-A review. *Nucleosides Nucleotides Nucleic Acids* **36**: 7-30 [PMID:27759477]
Pastor-Anglada M *et al.* (2015) Nucleoside transporter proteins as biomarkers of drug responsiveness and drug targets. *Front Pharmacol* **6**: 13 [PMID:25713533]
Young JD. (2016) The SLC28 (CNT) and SLC29 (ENT) nucleoside transporter families: a 30-year collaborative odyssey. *Biochem Soc Trans* **44**: 869-76 [PMID:27284054]
Young JD *et al.* (2013) The human concentrative and equilibrative nucleoside transporter families, SLC28 and SLC29. *Mol Aspects Med* **34**: 529-47 [PMID:23506887]

# SLC30 zinc transporter family

Transporters → SLC superfamily of solute carriers → SLC30 zinc transporter family

**Overview**: Along with the SLC39 family, SLC30 transporters regulate the movement of zinc ions around the cell. In particular, these transporters remove zinc ions from the cytosol, allowing accumulation into intracellular compartments or efflux through the plasma membrane. ZnT1 is thought to be placed on the plasma membrane extruding zinc, while ZnT3 is associated with synaptic vesicles and ZnT4 and ZnT5 are linked with secretory granules. Membrane topology predictions suggest a multimeric assembly, potentially heteromultimeric [688], with subunits having six TM domains, and both termini being cytoplasmic. Dityrosine covalent linking has been suggested as a mechanism for dimerisation, particularly for ZnT3 [637]. The mechanism for zinc transport is unknown.

Information on members of this family may be found in the online database.

**Comments**: ZnT8/SLC30A8 is described as a type 1 diabetes susceptibility gene.

Zinc fluxes may be monitored through the use of radioisotopic Zn-65 or the fluorescent dye FluoZin 3.

**Further reading on SLC30 zinc transporter family**

Bouron A *et al.* (2014) Contribution of calcium-conducting channels to the transport of zinc ions. *Pflugers Arch* **466**: 381-7 [PMID:23719866]
Hojyo S *et al.* (2016) Zinc transporters and signaling in physiology and pathogenesis. *Arch Biochem Biophys* **611**: 43-50 [PMID:27394923]
Huang L *et al.* (2013) The SLC30 family of zinc transporters - a review of current understanding of their biological and pathophysiological roles. *Mol Aspects Med* **34**: 548-60 [PMID:23506888]
Kambe T *et al.* (2014) Current understanding of ZIP and ZnT zinc transporters in human health and diseases. *Cell Mol Life Sci* **71**: 3281-95 [PMID:24710731]
Kambe T *et al.* (2015) The Physiological, Biochemical, and Molecular Roles of Zinc Transporters in Zinc Homeostasis and Metabolism. *Physiol Rev* **95**: 749-784 [PMID:26084690]

# SLC31 family of copper transporters

Transporters → SLC superfamily of solute carriers → SLC31 family of copper transporters

**Overview**: SLC31 family members, alongside the Cu-ATPases are involved in the regulation of cellular copper levels. The CTR1 transporter is a cell-surface transporter to allow monovalent copper accumulation into cells, while CTR2 appears to be a vacuolar/vesicular transporter [602]. Functional copper transporters appear to be trimeric with each subunit having three TM regions and an extracellular N-terminus. CTR1 is considered to be a higher affinity copper transporter compared to CTR2. The stoichiometry of copper accumulation is unclear, but appears to be energy-independent [443].

| | | |
|---|---|---|
| Nomenclature | Copper transporter 1 | Copper transporter 2 |
| Systematic nomenclature | SLC31A1 | SLC31A2 |
| Common abbreviation | CTR1 | CTR2 |
| HGNC, UniProt | *SLC31A1*, O15431 | *SLC31A2*, O15432 |
| Substrates | cisplatin [362] | cisplatin [71] |
| Endogenous substrates | copper [443] | copper |
| Stoichiometry | Unknown | Unknown |

**Comments**: Copper accumulation through CTR1 is sensitive to silver ions, but not divalent cations [443].

**Further reading on SLC31 family of copper transporters**

Howell SB *et al.* (2010) Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. *Mol Pharmacol* **77**: 887-94 [PMID:20159940]
Kaplan JH *et al.* (2016) How Mammalian Cells Acquire Copper: An Essential but Potentially Toxic Metal. *Biophys J* **110**: 7-13 [PMID:26745404]
Kim H *et al.* (2013) SLC31 (CTR) family of copper transporters in health and disease. *Mol Aspects Med* **34**: 561-70 [PMID:23506889]
Monné M *et al.* (2014) Antiporters of the mitochondrial carrier family. *Curr Top Membr* **73**: 289-320 [PMID:24745987]

# SLC32 vesicular inhibitory amino acid transporter

Transporters → SLC superfamily of solute carriers → SLC32 vesicular inhibitory amino acid transporter

**Overview**: The vesicular inhibitory amino acid transporter, VIAAT (also termed the vesicular GABA transporter VGAT), which is the sole representative of the SLC32 family, transports GABA, or glycine, into synaptic vesicles [254, 255], and is a member of the structurally-defined amino acid-polyamine-or-ganocation/APC clan composed of SLC32, SLC36 and SLC38 transporter families (see [645]). VIAAT was originally suggested to be composed of 10 TM segments with cytoplasmic N- and C-termini [496]. However, an alternative 9TM structure with the N terminus facing the cytoplasm and the C terminus residing in the synaptic vesicle lumen has subsequently been reported [493]. VIAAT acts as an antiporter for inhibitory amino acids and protons. The accumulation of GABA and glycine within vesicles is driven by both the chemical (ΔpH) and electrical ($\Delta\psi$) components of the proton electrochemical gradient ($\Delta\mu_{H}+$) established by a vacuolar $H^+$-ATPase [496]. However, one study, [382], presented evidence that VIAAT is instead a $Cl^-$/GABA co-transporter. VIAAT co-exists with VGLUT1 (SLC17A7), or VGLUT2 (SLC17A6), in the synaptic vesicles of selected nerve terminals [214, 834]. VIAAT knock out mice die between embryonic day 18.5 and birth [791]. In cultures of spinal cord neurones established from earlier embryos, the co-release of of GABA and glycine from synaptic vesicles is drastically reduced, providing direct evidence for the role of VIAAT in the sequestration of both transmitters [633, 791].

| | |
|---|---|
| Nomenclature | Vesicular inhibitory amino acid transporter |
| Systematic nomenclature | SLC32A1 |
| Common abbreviation | VIAAT |
| HGNC, UniProt | *SLC32A1*, Q9H598 |
| Endogenous substrates | GABA ($K_m$ $5 \times 10^{-3}$M) [496], glycine, β-alanine, γ-hydroxybutyric acid |
| Stoichiometry | 1 amino acid (in): 1 $H^+$ (out) [255] or 1 amino acid: 2$Cl^-$ (in) [382] |
| Inhibitors | vigabatrin ($pIC_{50}$ 2.1) [496] |

**Further reading on SLC32 vesicular inhibitory amino acid transporter**

Anne C *et al.* (2014) Vesicular neurotransmitter transporters: mechanistic aspects. *Curr Top Membr* **73**: 149-74 [PMID:24745982]

Schiöth HB *et al.* (2013) Evolutionary origin of amino acid transporter families SLC32, SLC36 and SLC38 and physiological, pathological and therapeutic aspects. *Mol Aspects Med* **34**: 571-85 [PMID:23506890]

# SLC33 acetylCoA transporter

Transporters → SLC superfamily of solute carriers → SLC33 acetylCoA transporter

**Overview**: Acetylation of proteins is a post-translational modification mediated by specific acetyltransferases, using the donor acetyl CoA. SLC33A1/AT1 is a putative 11 TM transporter present on the endoplasmic reticulum, expressed in all tissues, but particularly abundant in the pancreas [390], which imports cytosolic acetyl CoA into these intracellular organelles.

| | |
|---|---|
| Nomenclature | AcetylCoA transporter |
| Systematic nomenclature | SLC33A1 |
| Common abbreviation | ACATN1 |
| HGNC, UniProt | *SLC33A1*, O00400 |
| Endogenous substrates | acetyl CoA |
| Stoichiometry | Unknown |
| Labelled ligands | [$^{14}$C]acetylCoA (Binding) |

**Comments**: In heterologous expression studies, acetyl CoA transport through AT1 was inhibited by coenzyme A, but not acetic acid, ATP or UDP-galactose [378]. A loss-of-function mutation in ACATN1/SLC33A1 has been associated with spastic paraplegia (SPG42, [460]), although this observation could not be replicated in a subsequent study [647].

**Further reading on SLC33 acetylCoA transporter**

Hirabayashi Y *et al.* (2004) The acetyl-CoA transporter family SLC33. *Pflugers Arch* **447**: 760-2 [PMID:12739170]

Hirabayashi Y *et al.* (2013) The acetyl-CoA transporter family SLC33. *Mol Aspects Med* **34**: 586-9 [PMID:23506891]

# SLC34 family of sodium phosphate co-transporters

Transporters → SLC superfamily of solute carriers → SLC34 family of sodium phosphate co-transporters

**Overview**: The SLC34 family are sometimes referred to as Type II sodium-phosphate co-transporters, alongside Type I (SLC17 family) and Type III (SLC20 family) transporters. Topological modelling suggests eight TM domains with C- and N- termini in the cytoplasm, and a re-entrant loop at TM7/8. SLC34 family members are expressed on the apical surfaces of epithelia in the intestine and kidneys to regulate body phosphate levels, principally NaPi-IIa and NaPi-IIb, respectively. NaPi-IIa and NaPi-IIb are electrogenic, while NaPiIIc is electroneutral [24].

| | | | |
|---|---|---|---|
| Nomenclature | Sodium phosphate 1 | Sodium phosphate 2 | Sodium phosphate 3 |
| Systematic nomenclature | SLC34A1 | SLC34A2 | SLC34A3 |
| Common abbreviation | NaPi-IIa | NaPi-IIb | NaPi-IIc |
| HGNC, UniProt | *SLC34A1*, Q06495 | *SLC34A2*, O95436 | *SLC34A3*, Q8N130 |
| Stoichiometry | 3 $Na^+$ : 1 $HPO_4^{2-}$ (in) [232] | 3 $Na^+$ : 1 $HPO_4^{2-}$(in) [24] | 2 $Na^+$ : 1 $HPO_4^{2-}$ (in) [24] |
| Inhibitors | – | compound 15 ($pIC_{50}$ 7.2) [486] | – |
| Antibodies | – | lifastuzumab vedotin (Binding) [163] | – |
| Comments | – | NaPi2b is highly expressed by ovarian and non-small cell lung cancer (NSCLC) carcinomas, and is being actively pursued as a drug target for these tumours. XMT-1536 (Mersana Therapeutics) has entered Phase 1 proof-of-concept trial NCT03319628. Lifastuzumab vedotin (Genentech) reached Phase 2 evaluation, but trial NCT01991210 was terminated as the test agent failed to increase progression-free survival compared to standard-of-care pegylated liposomal doxorubicin, in ovarian cancer patients [50]. XMT-1536 and lifastuzumab vedotin are NaPi2b-directed monoclonal antibody-drug conjugates (ADCs). | – |

**Comments**: These transporters can be inhibited by foscarnet, in contrast to type III sodium-phosphate cotransporters, the SLC20 family.

**Further reading on SLC34 family of sodium phosphate co-transporters**

Biber J *et al.* (2013) Phosphate transporters and their function. *Annu Rev Physiol* **75**: 535-50 [PMID:23398154]
Forster IC *et al.* (2013) Phosphate transporters of the SLC20 and SLC34 families. *Mol Aspects Med* **34**: 386-95 [PMID:23506879]
Shobeiri N *et al.* (2014) Phosphate: an old bone molecule but new cardiovascular risk factor. *Br J Clin Pharmacol* **77**: 39-54 [PMID:23506202]
Wagner CA *et al.* (2014) The SLC34 family of sodium-dependent phosphate transporters. *Pflugers Arch* **466**: 139-53 [PMID:24352629]

# SLC35 family of nucleotide sugar transporters

Transporters → SLC superfamily of solute carriers → SLC35 family of nucleotide sugar transporters

**Overview**: Glycoprotein formation in the Golgi and endoplasmic reticulum relies on the accumulation of nucleotide-conjugated sugars via the SLC35 family of transporters. These transporters have a predicted topology of 10 TM domains, with cytoplasmic termini, and function as exchangers, swopping nucleoside monophosphates for the corresponding nucleoside diphosphate conjugated sugar. Five subfamilies of transporters have been identified on the basis of sequence similarity, namely SLC35A1, SLC35A2, SLC35A3, SLC35A4 and SLC35A5; SLC35B1, SLC35B2, SLC35B3 and SLC35B4; SLC35C1 and SLC35C2; SLC35D1, SL35D1, SLC35D2 and SLC35D3, and the subfamily of orphan SLC35 transporters, SLC35E1-4 and SLC35F1-5.

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | CMP-sialic acid transporter | UDP-galactose transporter | UDP-N-acetylglucosamine transporter | PAPS transporter 1 | PAPS transporter 2 |
| Systematic nomenclature | SLC35A1 | SLC35A2 | SLC35A3 | SLC35B2 | SLC35B3 |
| HGNC, UniProt | *SLC35A1*, P78382 | *SLC35A2*, P78381 | *SLC35A3*, Q9Y2D2 | *SLC35B2*, Q8TB61 | *SLC35B3*, Q9H1N7 |
| Substrates | CMP-sialic acid [358] | UDP N-acetyl-glucosamine [360, 513], UDP-galactose [360, 513] | UDP N-acetyl-glucosamine [361] | A3P5PS [385] | A3P5PS [384] |

| | | | | |
|---|---|---|---|---|
| Nomenclature | YEA | GDP-Fucose transporter | UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter | HFRC1 |
| Systematic nomenclature | SLC35B4 | SLC35C1 | SLC35D1 | SLC35D2 |
| HGNC, UniProt | *SLC35B4*, Q969S0 | *SLC35C1*, Q96A29 | *SLC35D1*, Q9NTN3 | *SLC35D2*, Q76EJ3 |
| Substrates | UDP N-acetyl-glucosamine [35], UDP-xylose [35] | GDP-fucose [477] | UDP-glucuronic acid [524], UDP-N-acetylgalactosamine [524] | UDP-N-acetylgalactosamine [359] |

**Further reading on SLC35 family of nucleotide sugar transporters**

Ishida N *et al.* (2004) Molecular physiology and pathology of the nucleotide sugar transporter family (SLC35). *Pflugers Arch* **447**: 768-75 [PMID:12759756]

Orellana A *et al.* (2016) Overview of Nucleotide Sugar Transporter Gene Family Functions Across Multiple Species. *J Mol Biol* **428**: 3150-3165 [PMID:27261257]

Song Z. (2013) Roles of the nucleotide sugar transporters (SLC35 family) in health and disease. *Mol Aspects Med* **34**: 590-600 [PMID:23506892]

# SLC36 family of proton-coupled amino acid transporters

Transporters → SLC superfamily of solute carriers → SLC36 family of proton-coupled amino acid transporters

**Overview**: Members of the SLC36 family of proton-coupled amino acid transporters are involved in membrane transport of amino acids and derivatives [722, 723]. The four transporters show variable tissue expression patterns and are expressed in various cell types at the plasma-membrane and in intracellular organelles. PAT1 is expressed at the luminal surface of the small intestine and absorbs amino acids and derivatives [20]. In lysosomes, PAT1 functions as an efflux mechanism for amino acids produced during intralysosomal proteolysis [6, 628]. PAT2 is expressed at the apical membrane of the renal proximal tubule [94] and at the plasma-membrane in brown/beige adipocytes [742]. PAT1 and PAT4 are involved in regulation of the mTORC1 pathway [211, 656]. More comprehensive lists of substrates can be found within the reviews under Further Reading and in the references [11].

| | | |
|---|---|---|
| Nomenclature | Proton-coupled Amino acid Transporter 1 | Proton-coupled Amino acid Transporter 2 |
| Systematic nomenclature | SLC36A1 | SLC36A2 |
| Common abbreviation | PAT1 | PAT2 |
| HGNC, UniProt | *SLC36A1*, Q7Z2H8 | *SLC36A2*, Q495M3 |
| Substrates | MeAIB [723], vigabatrin [1, 723], L-azetidine-2-carboxylate [723], gaboxadol [439, 723], THPO [723], betaine [723], β-guanidinopropionic acid [723], 5-aminolevulinic acid [723], L-cycloserine [723], muscimol [723], arecaidine [723], D-cycloserine [723], nicotianamine-Fe (II) complex [525] | MeAIB [122], L-azetidine-2-carboxylate [399], L-cycloserine, D-cycloserine |
| Endogenous substrates | taurine [723], β-alanine [723], GABA [723], D-serine [723], D-alanine [723], sarcosine [723], L-alanine [723], D-cysteine [723], glycine [723], trans-4-hydroxy-proline [723], D-proline [723] | glycine, L-proline, trans-4-hydroxy-proline, L-alanine, sarcosine |
| Stoichiometry | 1 $H^+$ : 1 amino acid (symport) | 1 $H^+$ : 1 amino acid (symport) |

| | | |
|---|---|---|
| Inhibitors | 17$\beta$-estradiol ($pIC_{50}$ 5–5.2) [541], ethinylestradiol ($pIC_{50}$ 4.3–4.6) [541], 5-hydroxy-L-tryptophan ($pK_i$ 3) [501], L-tryptophan ($pK_i$ 2.3) [501], indole-3-propionic acid ($pK_i$ 2.3) [501], 5-hydroxytryptamine ($pK_i$ 2.2) [501] | 5-hydroxy-L-tryptophan ($pIC_{50}$ 2.8) [190], $\alpha$-methyl-D,L-tryptophan ($pIC_{50}$ 2.5) [190] |
| Comments | [$^3$H] or [$^{14}$C] labelled substrates as listed above are used as probes. PAT1 can also function as an electroneutral transport system for protons and short chain fatty acids including acetic acid, propanoic acid and butyric acid [228]. In addition, forskolin, phosphodiesterase inhibitors, amiloride analogues and SLC9A3 (NHE3) selective inhibitors all reduce PAT1 activity indirectly (in intact mammalian intestinal epithelia such as human intestinal Caco-2 cells) by inhibiting the $Na^+/H^+$ exchanger NHE3 which is required to maintain the $H^+$-electrochemical gradient driving force for $H^+$/amino acid cotransport [20, 23, 723]. | [$^3$H] or [$^{14}$C] labelled substrates as listed above are used as probes. Loss-of-function mutations in PAT2 lead to iminoglycinuria and hyperglycinuria in man [94]. PAT2 can also function as an electroneutral transport system for protons and fatty acids including acetic acid, propanoic acid and butyric acid [228]. Replacement of a Phe residue in transmembrane domain 3 with Cys (that has a smaller side-chain) broadens substrate specificity to include larger substrates (*e.g.* methionine, leucine) [191]. |

| | | |
|---|---|---|
| Nomenclature | Proton-coupled Amino acid Transporter 3 | Proton-coupled Amino acid Transporter 4 |
| Systematic nomenclature | SLC36A3 | SLC36A4 |
| Common abbreviation | PAT3 | PAT4 |
| HGNC, UniProt | *SLC36A3*, Q495N2 | *SLC36A4*, Q6YBV0 |
| Endogenous substrates | – | L-tryptophan [578], L-proline [578] |
| Stoichiometry | Unknown | Unknown |
| Comments | The function of the testes-specific PAT3 remains unknown. | PAT4 is not proton-coupled and functions by facilitated diffusion in an electroneutral, $Na^+$-independent, manner [578]. PAT4 is expressed ubiquitously and is predominantly associated with the Golgi [212]. High PAT4 expression is associated with reduced relapse-free survival after colorectal cancer surgery [212]. |

**Comments**: The SLC36 transporters are part of the Amino Acid Auxin Permease (AAAP) family within the Amino Acid-Polyamine-Organocation (APC) superfamily [645, 755]. In neuronal tissues, PAT1 is found predominantly in lysosomal membranes and to a lesser extent on neuronal plasma membranes [6, 628, 794]. PAT1 acts as a driver of mTORC1 signalling, contributing CDK4/6 inhibitor resistance in melanoma [829]. PAT2 is found in myelinated fibres and in the endoplasmic reticulum in spinal cord and brain [60, 622]. In brown adipocytes, PAT2 acts as an extracellular amino acid sensor and regulates lysosomal acidification [771]. PAT4 is found in lysosomes in neurones and the plasma membrane of epithelial cells lining the lateral ventricles [617]. High PAT4 expression is associated with reduced relapse-free survival after colorectal cancer surgery [212]. Inhibition of SLC36 transporters by indole-3-propionic acid suppresses proline-dependent tumour growth in *Drosophila melanogaster* [537]. In *C. elegans*, a SLC36 transporter is involved in lysosome reformation pathways [216, 244].

### Further reading on SLC36 family of proton-coupled amino acid transporters

Schiöth HB *et al.* (2013) Evolutionary origin of amino acid transporter families SLC32, SLC36 and SLC38 and physiological, pathological and therapeutic aspects. *Mol Aspects Med* **34**: 571-85 [PMID:23506890]

Thwaites DT *et al.* (2007) Deciphering the mechanisms of intestinal imino (and amino) acid transport: the redemption of SLC36A1. *Biochim Biophys Acta* **1768**: 179-97 [PMID:17123464]

Thwaites DT *et al.* (2011) The SLC36 family of proton-coupled amino acid transporters and their potential role in drug transport. *Br J Pharmacol* **164**: 1802-16 [PMID:21501141]

# SLC37 family of phosphosugar/phosphate exchangers

Transporters → SLC superfamily of solute carriers → SLC37 family of phosphosugar/phosphate exchangers

**Overview**: The family of sugar-phosphate exchangers pass particular phosphorylated sugars across intracellular membranes, exchanging for inorganic phosphate. Of the family of sugar phosphate transporters, most information is available on SPX4, the glucose-6-phosphate transporter. This is a 10 TM domain protein with cytoplasmic termini and is associated with the endoplasmic reticulum, with tissue-specific splice variation.

| | | | |
|---|---|---|---|
| Nomenclature | Glycerol-3-phosphate transporter | Sugar phosphate exchanger 2 | Glucose-6-phosphate transporter |
| Systematic nomenclature | SLC37A1 | SLC37A2 | SLC37A4 |
| Common abbreviation | SPX1 | SPX2 | SPX4 |
| HGNC, UniProt | *SLC37A1*, P57057 | *SLC37A2*, Q8TED4 | *SLC37A4*, O43826 |
| Endogenous substrates | glycerol 3-phosphate, glucose 6-phosphate | glucose 6-phosphate | glucose 6-phosphate |
| Stoichiometry | Glucose 6-phosphate (in): phosphate (out) [567]. | Glucose 6-phosphate (in): phosphate (out) [567]. | Glucose 6-phosphate (in): phosphate (out) [120]. |
| Inhibitors | – | – | S-4048 ($pIC_{50}$ 8.7) [114] – Rat |
| Comments | – | – | Multiple polymorphisms have been described for the SLC37A4 gene, some of which associate with a glycogen storage disease [14]. |

**Further reading on SLC37 family of phosphosugar/phosphate exchangers**

Chou JY *et al.* (2014) The SLC37 family of sugar-phosphate/phosphate exchangers. *Curr Top Membr* **73**: 357-82 [PMID:24745989]

Chou JY *et al.* (2013) The SLC37 family of phosphate-linked sugar phosphate antiporters. *Mol Aspects Med* **34**: 601-11 [PMID:23506893]

# SLC38 family of sodium-dependent neutral amino acid transporters

Transporters → SLC superfamily of solute carriers → SLC38 family of sodium-dependent neutral amino acid transporters

**Overview**: The SLC38 family of transporters appears to be responsible for the functionally-defined system A and system N mechanisms of amino acid transport and are mostly expressed in the CNS. Two distinct subfamilies are identifiable within the SLC38 transporters. SNAT1, SNAT2 and SNAT4 appear to resemble system A transporters in accumulating neutral amino acids under the influence of the sodium gradient. SNAT3 and SNAT5 appear to resemble system N transporters in utilizing proton co-transport to accumulate amino acids. The predicted membrane topology is of 11 TM domains with an extracellular C-terminus and intracellular N-terminus [645].

# System A-like transporters

Transporters → SLC superfamily of solute carriers → SLC38 family of sodium-dependent neutral amino acid transporters → System A-like transporters

| | | | |
|---|---|---|---|
| Nomenclature | sodium-coupled neutral amino acid transporter 1 | sodium-coupled neutral amino acid transporter 2 | sodium-coupled neutral amino acid transporter 4 |
| Systematic nomenclature | SLC38A1 | SLC38A2 | SLC38A4 |
| Common abbreviation | SNAT1 | SNAT2 | SNAT4 |
| HGNC, UniProt | *SLC38A1*, Q9H2H9 | *SLC38A2*, Q96QD8 | *SLC38A4*, Q969I6 |
| Substrates | MeAIB<br>L-alanine > L-serine, L-glutamine, L-asparagine, L-histidine, L-cysteine, L-methionine > glycine, L-threonine, L-proline, L-tyrosine, L-valine [8] | MeAIB<br>L-alanine, L-methionine > L-asparagine, L-glutamine, L-serine, L-proline, glycine > L-threonine, L-leucine, L-phenylalanine [325] | MeAIB<br>L-histidine > L-arginine, L-alanine, L-asparagine, L-lysine > glycine, L-glutamine, L-serine, L-proline, L-leucine, L-phenylalanine [324] |
| Stoichiometry | 1 $Na^+$ : 1 amino acid (in) [8] | 1 $Na^+$ : 1 amino acid (in) [325] | 1 $Na^+$ : 1 neutral amino acid (in) [324] |
| Labelled ligands | [$^{14}$C]alanine, [$^{3}$H]alanine | [$^{14}$C]alanine, [$^{3}$H]alanine | [$^{14}$C]alanine, [$^{14}$C]glycine, [$^{3}$H]alanine, [$^{3}$H]glycine |
| Comments | – | – | Transport of cationic amino acids by SNAT4 was sodium-independent [324]. |

# System N-like transporters

Transporters → SLC superfamily of solute carriers → SLC38 family of sodium-dependent neutral amino acid transporters → System N-like transporters

| | | |
|---|---|---|
| Nomenclature | Sodium-coupled neutral amino acid transporter 3 | Sodium-coupled neutral amino acid transporter 5 |
| Systematic nomenclature | SLC38A3 | SLC38A5 |
| Common abbreviation | SNAT3 | SNAT5 |
| HGNC, UniProt | *SLC38A3*, Q99624 | *SLC38A5*, Q8WUX1 |
| Substrates | MeAIB<br>L-histidine , L-glutamine > L-asparagine, L-alanine > L-glutamic acid [218] | MeAIB<br>L-asparagine, L-serine, L-histidine, L-glutamine > glycine, L-alanine [532] |
| Stoichiometry | 1 $Na^+$ : 1 amino acid (in) : 1 $H^+$ (out) [87] | 1 $Na^+$ : 1 amino acid (in) : 1 $H^+$ (out) [532] |
| Labelled ligands | [$^{14}$C]glutamine, [$^{3}$H]glutamine | [$^{14}$C]histidine, [$^{3}$H]histidine |

# Orphan SLC38 transporters

Transporters → SLC superfamily of solute carriers → SLC38 family of sodium-dependent neutral amino acid transporters → Orphan SLC38 transporters

| | |
|---|---|
| Nomenclature | Putative sodium-coupled neutral amino acid transporter 7 |
| Systematic nomenclature | SLC38A7 |
| Common abbreviation | SNAT7 |
| HGNC, UniProt | *SLC38A7*, Q9NVC3 |
| Comments | SNAT7/SLC38A7 has been described to be a system N-like transporter allowing preferential accumulation of glutamine (*e.g.* L-glutamine), histidine (*e.g.* L-histidine) and asparagine (*e.g.* L-asparagine) [313]. |

**Further reading on SLC38 family of sodium-dependent neutral amino acid transporters**

Bhutia YD *et al.* (2016) Glutamine transporters in mammalian cells and their functions in physiology and cancer. *Biochim Biophys Acta* **1863**: 2531-9 [PMID:26724577]
Bröer S. (2014) The SLC38 family of sodium-amino acid co-transporters. *Pflugers Arch* **466**: 155-72 [PMID:24193407]
Bröer S *et al.* (2011) The role of amino acid transporters in inherited and acquired diseases. *Biochem J* **436**: 193-211 [PMID:21568940]
Hägglund MG *et al.* (2011) Identification of SLC38A7 (SNAT7) protein as a glutamine transporter expressed in neurons. *J Biol Chem* **286**: 20500-11 [PMID:21511949]
Schiöth HB *et al.* (2013) Evolutionary origin of amino acid transporter families SLC32, SLC36 and SLC38 and physiological, pathological and therapeutic aspects. *Mol Aspects Med* **34**: 571-85 [PMID:23506890]

# SLC39 family of metal ion transporters

Transporters → SLC superfamily of solute carriers → SLC39 family of metal ion transporters

**Overview**: Along with the SLC30 family, SLC39 family members regulate zinc movement in cells. SLC39 metal ion transporters accumulate zinc into the cytosol. Membrane topology modelling suggests the presence of eight TM regions with both termini extracellular or in the lumen of intracellular organelles. The mechanism for zinc transport for many members is unknown but appears to involve co-transport of bicarbonate ions [268, 467].

| | | |
|---|---|---|
| Nomenclature | Zinc transporter 8 | Zinc transporter 14 |
| Systematic nomenclature | SLC39A8 | SLC39A14 |
| Common abbreviation | ZIP8 | ZIP14 |
| HGNC, UniProt | *SLC39A8*, Q9C0K1 | *SLC39A14*, Q15043 |
| Substrates | $Cd^{2+}$ [149, 467] | $Cd^{2+}$ [268], $Mn^{2+}$ [268], $Fe^{2+}$ [469] |
| Stoichiometry | 1 $Zn^{2+}$ (in) : 2 $HCO_3^-$ (in) [467] | – |

**Comments**: Zinc fluxes may be monitored through the use of radioisotopic Zn-65 or the fluorescent dye FluoZin 3.

The bicarbonate transport inhibitor DIDS has been reported to inhibit cation accumulation through ZIP14 [268].

**Further reading on SLC39 family of metal ion transporters**

Hojyo S *et al.* (2016) Zinc transporters and signaling in physiology and pathogenesis. *Arch Biochem Biophys* **611**: 43-50 [PMID:27394923]
Jeong J *et al.* (2013) The SLC39 family of zinc transporters. *Mol Aspects Med* **34**: 612-9 [PMID:23506894]
Kambe T *et al.* (2014) Current understanding of ZIP and ZnT zinc transporters in human health and diseases. *Cell Mol Life Sci* **71**: 3281-95 [PMID:24710731]
Kambe T *et al.* (2015) The Physiological, Biochemical, and Molecular Roles of Zinc Transporters in Zinc Homeostasis and Metabolism. *Physiol Rev* **95**: 749-784 [PMID:26084690]
Marger L *et al.* (2014) Zinc: an underappreciated modulatory factor of brain function. *Biochem Pharmacol* **91**: 426-35 [PMID:25130547]

# SLC40 iron transporter

Transporters → SLC superfamily of solute carriers → SLC40 iron transporter

**Overview**: Alongside the SLC11 family of proton-coupled metal transporters, ferroportin allows the accumulation of iron from the diet. Whilst SLC11A2 functions on the apical membrane, ferroportin acts on the basolateral side of the enterocyte, as well as regulating macrophage and placental iron levels. The predicted topology is of 12 TM domains, with intracellular termini [608], with the functional transporter potentially a dimeric arrangement [5, 157]. Ferroportin is essential for iron homeostasis [178]. Ferroportin is expressed on the surface of cells that store and transport iron, such as duodenal enterocytes, hepatocytes, adipocytes and reticuloendothelial macrophages. Levels of ferroportin are regulated by its association with (binding to) hepcidin, a 25 amino acid hormone responsive to circulating iron levels (amongst other signals). Hepcidin binding targets ferroportin for internalisation and degradation, lowering the levels of iron export to the blood. Novel therapeutic agents which stabilise ferroportin or protect it from hepcidin-induced degradation are being developed as anti-anemia agents. Anti-ferroportin monoclonal antibodies are such an agent.

| | |
|---|---|
| Nomenclature | Ferroportin |
| Systematic nomenclature | SLC40A1 |
| Common abbreviation | IREG1 |
| HGNC, UniProt | *SLC40A1*, Q9NP59 |
| Endogenous substrates | $Fe^{2+}$ |
| Stoichiometry | Unknown |
| Antibodies | LY2928057 (Binding) [453] |

**Comments**: Hepcidin (HAMP, P81172), cleaved into hepcidin-25 (HAMP, P81172) and hepcidin-20 (HAMP, P81172), is a small protein that increases upon inflammation, binds to ferroportin to regulate its cellular distribution and degradation. Gene disruption in mice results in embryonic lethality [178], while loss-of-function mutations in man are associated with haemochromatosis [158].

**Further reading on SLC40 iron transporter**

McKie AT *et al.* (2004) The SLC40 basolateral iron transporter family (IREG1/ferroportin/MTP1). *Pflugers Arch* **447**: 801-6 [PMID:12836025]
Montalbetti N *et al.* (2013) Mammalian iron transporters: families SLC11 and SLC40. *Mol Aspects Med* **34**: 270-87 [PMID:23506870]

# SLC41 family of divalent cation transporters

Transporters → SLC superfamily of solute carriers → SLC41 family of divalent cation transporters

**Overview**: By analogy with bacterial orthologues, this family is probably magnesium transporters. The prokaryote orthologue, MgtE, is responsible for uptake of divalent cations, while the heterologous expression studies of mammalian proteins suggest $Mg^{2+}$ efflux [420], possibly as a result of co-expression of particular protein partners (see [629]). Topological modelling suggests 10 TM domains with cytoplasmic C- and N- termini.

| | | |
|---|---|---|
| Nomenclature | Solute carrier family 41 member 1 | Solute carrier family 41 member 2 |
| Systematic nomenclature | SLC41A1 | SLC41A2 |
| Common abbreviation | MgtE | – |
| HGNC, UniProt | *SLC41A1*, Q8IVJ1 | *SLC41A2*, Q96JW4 |
| Substrates | $Zn^{2+}$ [284], $Mg^{2+}$ [284], $Ba^{2+}$ [284], $Cd^{2+}$ [284], $Co^{2+}$ [284], $Cu^{2+}$ [284], $Sr^{2+}$ [284], $Fe^{2+}$ [284] | $Mg^{2+}$ [285], $Ba^{2+}$ [285], $Ni^{2+}$ [285], $Co^{2+}$ [285], $Mn^{2+}$ [285], $Fe^{2+}$ [285] |
| Stoichiometry | Unknown | Unknown |

**Further reading on SLC41 family of divalent cation transporters**

Payandeh J *et al.* (2013) The structure and regulation of magnesium selective ion channels. *Biochim Biophys Acta* **1828**: 2778-92 [PMID:23954807]

Sahni J *et al.* (2013) The SLC41 family of MgtE-like magnesium transporters. *Mol Aspects Med* **34**: 620-8 [PMID:23506895]

Schweigel-Röntgen M *et al.* (2014) SLC41 transporters–molecular identification and functional role. *Curr Top Membr* **73**: 383-410 [PMID:24745990]

# SLC42 family of Rhesus glycoprotein ammonium transporters

Transporters → SLC superfamily of solute carriers → SLC42 family of Rhesus glycoprotein ammonium transporters

**Overview**: Rhesus is commonly defined as a 'factor' that determines, in part, blood type, and whether neonates suffer from haemolytic disease of the newborn. These glycoprotein antigens derive from two genes, RHCE (P18577) and RHD (Q02161), expressed on the surface of erythrocytes. On erythrocytes, RhAG associates with these antigens and functions as an ammonium transporter. RhBG and RhBG are non-erythroid related sequences associated with epithelia. Topological modelling suggests the presence of 12TM with cytoplasmic N- and C- termini. The majority of information on these transporters derives from orthologues in yeast, plants and bacteria. More recent evidence points to family members being permeable to carbon dioxide, leading to the term gas channels.

| | | | |
|---|---|---|---|
| Nomenclature | Ammonium transporter Rh type A | Ammonium transporter Rh type B | Ammonium transporter Rh type C |
| Systematic nomenclature | SLC42A1 | SLC42A2 | SLC42A3 |
| Common abbreviation | RhAG | RhBG | RhCG |
| HGNC, UniProt | *RHAG*, Q02094 | *RHBG*, Q9H310 | *RHCG*, Q9UBD6 |
| Substrates | $CO_2$ [199], $NH_3$ [609], $NH_4^+$ [785] | – | $NH_3$ [855] |
| Stoichiometry | Unknown | Unknown | Unknown |
| Labelled ligands | [$^{14}$C]methylamine (Binding) [330] | – | [$^{14}$C]methylamine (Binding) [487] – Mouse |

**Further reading on SLC42 family of Rhesus glycoprotein ammonium transporters**

Nakhoul NL *et al.* (2013) Characteristics of mammalian Rh glycoproteins (SLC42 transporters) and their role in acid-base transport. *Mol Aspects Med* **34**: 629-37 [PMID:23506896]

Weiner ID *et al.* (2011) Role of NH3 and NH4+ transporters in renal acid-base transport. *Am J Physiol Renal Physiol* **300**: F11-23 [PMID:21048022]

Weiner ID *et al.* (2014) Ammonia transport in the kidney by Rhesus glycoproteins. *Am J Physiol Renal Physiol* **306**: F1107-20 [PMID:24647713]

# SLC43 family of large neutral amino acid transporters

Transporters → SLC superfamily of solute carriers → SLC43 family of large neutral amino acid transporters

**Overview**: LAT3 (SLC43A1) and LAT4 (SLC43A2) are transporters with system L amino acid transporter activity, along with the structurally and functionally distinct transporters LAT1 and LAT2 that are members of the SLC7 family. LAT3 and LAT4 contain 12 putative TM domains with both N and C termini located intracellularly. They transport neutral amino acids in a manner independent of $Na^+$ and $Cl^-$ and with two kinetic components [40, 74]. LAT3/SLC43A1 is expressed in human tissues at high levels in the pancreas, liver, skeletal muscle and fetal liver [40] whereas LAT4/SLC43A2 is primarily expressed in the placenta, kidney and peripheral blood leukocytes [74]. SLC43A3 is expressed in vascular endothelial cells [765] but remains to be characterised.

| | | |
|---|---|---|
| Nomenclature | L-type amino acid transporter 3 | L-type amino acid transporter 4 |
| Systematic nomenclature | SLC43A1 | SLC43A2 |
| Common abbreviation | LAT3 | LAT4 |
| HGNC, UniProt | *SLC43A1*, O75387 | *SLC43A2*, Q8N370 |
| Substrates | L-leucine [40], L-isoleucine [40], L-phenylalanine [40], L-valine [40], L-valinol [40], L-phenylalaninol [40], L-methionine [40], L-leucinol [40] | L-isoleucine, L-leucine, L-phenylalanine, L-valinol, L-leucinol, L-valine, L-methionine |
| Stoichiometry | Operates by facilitative diffusion | Operates by facilitative diffusion |

**Comments**: Covalent modification of LAT3 by N-ethylmaleimide inhibits its function [40] and at LAT4 inhibits the low-, but not high-affinity component of transport [74].

**Further reading on SLC43 family of large neutral amino acid transporters**

Bodoy S *et al.* (2013) The small SLC43 family: facilitator system l amino acid transporters and the orphan EEG1. *Mol Aspects Med* **34**: 638-45 [PMID:23268354]

# SLC44 choline transporter-like family

Transporters → SLC superfamily of solute carriers → SLC44 choline transporter-like family

**Overview**: Members of the choline transporter-like family are encoded by five genes (CTL1-CTL5) with further diversity occurring through alternative splicing of CTL1, 4 and 5 [728]. CTL family members are putative 10TM domain proteins with extracellular termini that mediate $Na^+$-independent transport of choline with an affinity that is intermediate to that of the high affinity choline transporter CHT1 (SLC5A7) and the low affinity organic-cation transporters [OCT1 (SLC22A1) and OCT2 (SLC22A2)] [505]. CLT1 is expressed almost ubiquitously in human tissues [789] and mediates choline transport across the plasma and mitochondrial membranes [504]. Transport of choline by CTL2, which in rodents is expressed as two isoforms (CTL2P1 and CLTP2; [421]) in lung, colon, inner ear and spleen and to a lesser extent in brain, tongue, liver, and kidney, has only recently been demonstrated [421, 531]. CTL3-5 remain to be characterized functionally.

| | |
|---|---|
| Nomenclature | Choline transporter-like 1 |
| Systematic nomenclature | SLC44A1 |
| Common abbreviation | CTL1 |
| HGNC, UniProt | *SLC44A1*, Q8WWI5 |
| Substrates | choline |
| Stoichiometry | Unknown: uptake enhanced in the absence of extracellular $Na^+$, reduced by membrane depolarization, extracellular acidification and collapse of plasma membrane $H^+$ electrochemical gradient |
| Inhibitors | hemicholinium-3 ($pK_i$ 3.5–4.5) |

**Comments**: Data tabulated are features observed for CLT1 endogenous to: rat astrocytes [352]; rat renal tubule epithelial cells [812]; human colon carcinoma cells [424]; human keratinocytes [738] and human neuroblastoma cells [814]. Choline uptake by CLT1 is inhibited by numerous organic cations (*e.g.* [352, 812, 814]). In the guinea-pig, CTL2 is a target for antibody-induced hearing loss [527] and in man, a polymorphism in CTL2 constitutes the human neutrophil alloantigen-3a (HNA-3a; [291]).

**Further reading on SLC44 choline transporter-like family**

Inazu M. (2014) Choline transporter-like proteins CTLs/SLC44 family as a novel molecular target for cancer therapy. *Biopharm Drug Dispos* **35**: 431-49 [PMID:24532461]

Traiffort E *et al.* (2013) The choline transporter-like family SLC44: properties and roles in human diseases. *Mol Aspects Med* **34**: 646-54 [PMID:23506897]

# SLC45 family of putative sugar transporters

Transporters → SLC superfamily of solute carriers → SLC45 family of putative sugar transporters

**Overview**: Members of the SLC45 family remain to be fully characterised. SLC45A1 was initially identified in the rat brain, particularly predominant in the hindbrain, as a proton-associated sugar transport, induced by hypercapnia [662]. The protein is predicted to have 12TM domains, with intracellular termini. The *SLC45A2* gene is thought to encode a transporter protein that mediates melanin synthesis. Mutations in *SLC45A2* are a cause of oculocutaneous albinism type 4 (*e.g.* [538]), and polymorphisms in this gene are associated with variations in skin and hair color (*e.g.* [287]).

| | |
|---|---|
| Nomenclature | Proton-associated sugar transporter A |
| Systematic nomenclature | SLC45A1 |
| HGNC, UniProt | *SLC45A1*, Q9Y2W3 |
| Substrates | L-glucose [662], Galactose [662] |
| Stoichiometry | Unknown; increased at acid pH [662]. |

**Further reading on SLC45 family of putative sugar transporters**

Bartölke R *et al.* (2014) Proton-associated sucrose transport of mammalian solute carrier family 45: an analysis in Saccharomyces cerevisiae. *Biochem J* **464**: 193-201 [PMID:25164149]

Vitavska O *et al.* (2013) The SLC45 gene family of putative sugar transporters. *Mol Aspects Med* **34**: 655-60 [PMID:23506898]

# SLC46 family of folate transporters

Transporters → SLC superfamily of solute carriers → SLC46 family of folate transporters

**Overview**: Based on the proptypical member of this family, PCFT, this family includes proton-driven transporters with 11 TM segments. SLC46A1 has been described to act as an intestinal proton-coupled high-affinity folic acid transporter [590], with lower affinity for heme. Folic acid accumulation is independent of $Na^+$ or $K^+$ ion concentrations, but driven by extracellular protons with an as yet undefined stoichiometry.

| | |
|---|---|
| Nomenclature | Proton-coupled folate transporter |
| Systematic nomenclature | SLC46A1 |
| Common abbreviation | PCFT |
| HGNC, UniProt | *SLC46A1*, Q96NT5 |
| Substrates | methotrexate [590], N-formyltetrahydrofolate, pemetrexed<br>folic acid (1.3$\mu$M) > heme (>100 $\mu$M) [528] |
| Endogenous substrates | $N^5$-methyltetrafolate [590] |
| Labelled ligands | [$^3$H]$N^5$-methylfolate (Binding), [$^3$H]folic acid, [$^3$H]folinic acid (Binding), [$^3$H]methotrexate, [$^3$H]pemetrexed (Binding) |
| Comments | Loss-of-function mutations in PCFT (SLC46A1) are the molecular basis for hereditary folate maladsorption [638]. |

**Further reading on SLC46 family of folate transporters**

Hou Z *et al.* (2014) Biology of the major facilitative folate transporters SLC19A1 and SLC46A1. *Curr Top Membr* **73**: 175-204 [PMID:24745983]

Matherly LH *et al.* (2014) The major facilitative folate transporters solute carrier 19A1 and solute carrier 46A1: biology and role in antifolate chemotherapy of cancer. *Drug Metab Dispos* **42**: 632-49 [PMID:24396145]

Wilson MR *et al.* (2015) Structural determinants of human proton-coupled folate transporter oligomerization: role of GXXXG motifs and identification of oligomeric interfaces at transmembrane domains 3 and 6. *Biochem J* **469**: 33-44 [PMID:25877470]

Zhao R *et al.* (2011) Mechanisms of membrane transport of folates into cells and across epithelia. *Annu Rev Nutr* **31**: 177-201 [PMID:21568705]

Zhao R *et al.* (2013) Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors. *Mol Aspects Med* **34**: 373-85 [PMID:23506878]

# SLC47 family of multidrug and toxin extrusion transporters

Transporters → SLC superfamily of solute carriers → SLC47 family of multidrug and toxin extrusion transporters

**Overview**: Human multidrug and toxin extrusion MATE1 and MATE2-K are $H^+$/organic cation antiporters [10]. They are predominantly expressed in the kidney and play a role in renal tubular secretion of cationic drugs.

| | | |
|---|---|---|
| Nomenclature | Multidrug and toxin extrusion | MATE2 |
| Systematic nomenclature | SLC47A1 | SLC47A2 |
| Common abbreviation | MATE1 | MATE2-K |
| HGNC, UniProt | *SLC47A1*, Q96FL8 | *SLC47A2*, Q86VL8 |
| Substrates | paraquat [121], quinidine [704], cephradine [704], cephalexin [704], cimetidine ($K_m$ $1.7 \times 10^{-4}$M) [554, 704], metformin ($K_m$ $7.8 \times 10^{-4}$M) [704] | $MPP^+$ [495], $N^1$-methylnicotinamide [495], procainamide [495], guanidine [704], aciclovir [704], cimetidine ($K_m$ $1.2 \times 10^{-4}$M) [495, 704], metformin ($K_m$ $1.9 \times 10^{-3}$M) [495, 704] |

| | | |
|---|---|---|
| Endogenous substrates | thiamine [704], creatine [704] | creatine [704], thiamine [704] |
| Sub/family-selective inhibitors | pyrimethamine ($pK_i$ 7.1) [365], cimetidine ($pK_i$ 6) [733] | pyrimethamine ($pK_i$ 6.3) [365] – Mouse, cimetidine ($pK_i$ 5.1) [733] |
| Labelled ligands | [$^{14}$C]TEA [561, 712], [$^{14}$C]metformin [704, 712] | [$^{14}$C]TEA [704], [$^{14}$C]metformin [704] |

**Comments**: DAPI has been used to allow quantification of MATE1 and MATE2-mediated transport activity [825]. MATE2 and MATE2-B are inactive splice variants of MATE2-K [495].

### Further reading on SLC47 family of multidrug and toxin extrusion transporters


Damme K *et al.* (2011) Mammalian MATE (SLC47A) transport proteins: impact on efflux of endogenous substrates and xenobiotics. *Drug Metab Rev* **43**: 499-523 [PMID:21923552]

Koepsell H. (2020) Organic Cation Transporters in Health and Disease. *Pharmacol Rev* **72**: 253-319 [PMID:31852803]

Krishnan S *et al.* (2022) Challenges and Opportunities for Improved Drug-Drug Interaction Predictions for Renal OCT2 and MATE1/2-K Transporters. *Clin Pharmacol Ther* **112**: 562-572 [PMID:35598119]

Motohashi H *et al.* (2013) Multidrug and toxin extrusion family SLC47: physiological, pharmacokinetic and toxicokinetic importance of MATE1 and MATE2-K. *Mol Aspects Med* **34**: 661-8 [PMID:23506899]

Yonezawa A *et al.* (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. *Br J Pharmacol* **164**: 1817-25 [PMID:21457222]


# SLC48 heme transporter

Transporters → SLC superfamily of solute carriers → SLC48 heme transporter

**Overview**: HRG1 has been identified as a cell surface and lysosomal heme transporter [598]. In addition, evidence suggests this 4TM-containing protein associates with the V-ATPase in lysosomes [550]. Recent studies confirm its lysosomal location and demonstrate that it has an important physiological function in macrophages ingesting senescent red blood cells (erythrophagocytosis), recycling heme (released from the red cell hemoglobin) from the phagolysosome into the cytosol, where the heme is subsequently catabolized to recycle the iron [786].

| | |
|---|---|
| Nomenclature | Heme transporter |
| Systematic nomenclature | SLC48A1 |
| Common abbreviation | HRG1 |
| HGNC, UniProt | *SLC48A1*, Q6P1K1 |

### Further reading on SLC48 heme transporter


Khan AA *et al.* (2013) Heme and FLVCR-related transporter families SLC48 and SLC49. *Mol Aspects Med* **34**: 669-82 [PMID:23506900]

# SLC49 family of FLVCR-related heme transporters

Transporters → SLC superfamily of solute carriers → SLC49 family of FLVCR-related heme transporters

**Overview**: FLVCR1 was initially identified as a cell-surface attachment site for feline leukemia virus subgroup C [693], and later identified as a cell surface accumulation which exports heme from the cytosol [594]. A recent study indicates that an isoform of FLVCR1 is located in the mitochondria, the site of the final steps of heme synthesis, and appears to transport heme into the cytosol [128]. FLVCR-mediated heme transport is essential for erythropoiesis. Flvcr1 gene mutations have been identified as the cause of PCARP (posterior column ataxia with retinitis pigmentosa (PCARP) [597]. There are three paralogs of FLVCR1 in the human genome.

FLVCR2, most similar to FLVCR1 [462], has been reported to function as a heme importer [183]. In addition, a congenital syndrome of proliferative vasculopathy and hydranencephaly, also known as Fowler's syndrome, is associated with a loss-of-function mutation in FLVCR2 [502].

The functions of the other two members of the SLC49 family, MFSD7 and DIRC2, are unknown, although DIRC2 has been implicated in hereditary renal carcinomas [73].

| | | |
|---|---|---|
| Nomenclature | Feline leukemia virus subgroup C cellular receptor family, member 1 | Feline leukemia virus subgroup C cellular receptor family, member 2 |
| Systematic nomenclature | SLC49A1 | SLC49A2 |
| Common abbreviation | FLVCR1 | FLVCR2 |
| HGNC, UniProt | *FLVCR1*, Q9Y5Y0 | *FLVCR2*, Q9UPI3 |
| Substrates | heme [594] | heme [183] |
| Stoichiometry | Unknown | Unknown |

**Comments**: Non-functional splice alternatives of FLVCR1 have been implicated as a cause of a congenital red cell aplasia, Diamond Blackfan anemia [606].

**Further reading on SLC49 family of FLVCR-related heme transporters**

Khan AA *et al.* (2011) Control of intracellular heme levels: heme transporters and heme oxygenases. *Biochim Biophys Acta* **1813**: 668-82 [PMID:21238504]

Khan AA *et al.* (2013) Heme and FLVCR-related transporter families SLC48 and SLC49. *Mol Aspects Med* **34**: 669-82 [PMID:23506900]

# SLC50 sugar transporter

Transporters → SLC superfamily of solute carriers → SLC50 sugar transporter

**Overview**: A mouse stromal cell cDNA library was used to clone C2.3 [690], later termed Rag1-activating protein 1, with a sequence homology predictive of a 4TM topology. The plant orthologues, termed SWEETs, appear to be 7 TM proteins, with extracellular N-termini, and the capacity for bidirectional flux of D-glucose [118]. Expression of mouse SWEET in the mammary gland was suggestive of a role in Golgi lactose synthesis [118].

| | |
|---|---|
| Nomenclature | SLC50 sugar exporter |
| Systematic nomenclature | SLC50A1 |
| Common abbreviation | RAG1AP1 |
| HGNC, UniProt | *SLC50A1*, Q9BRV3 |

**Further reading on SLC50 sugar transporter**

Wright EM. (2013) Glucose transport families SLC5 and SLC50. *Mol Aspects Med* **34**: 183-96 [PMID:23506865]

Wright EM *et al.* (2011) Biology of human sodium glucose transporters. *Physiol Rev* **91**: 733-94 [PMID:21527736]

# SLC51 family of steroid-derived molecule transporters

Transporters → SLC superfamily of solute carriers → SLC51 family of steroid-derived molecule transporters

**Overview**: The SLC51 organic solute transporter family of transporters is a pair of heterodimeric proteins which regulate bile salt movements in the small intestine, bile duct, and liver, as part of the enterohepatic circulation [11, 48, 154]. OST$\alpha$/OST$\beta$ is also expressed in steroidogenic cells of the brain and adrenal gland, where it may contribute to steroid sulphate movement [213]. Bile acid and steroid sulphate transport is suggested to be facilitative and independent of sodium, potassium, chloride ions or protons [48, 154]. OST$\alpha$/OST$\beta$ heterodimers have been shown to transport [$^3$H]taurocholic acid, [$^3$H]dehydroepiandrosterone sulphate, [$^3$H]estrone-3-sulphate, [$^3$H]pregnenolone sulphate and [$^3$H]dehydroepiandrosterone sulphate[48, 154, 213]. OST$\alpha$/OST$\beta$-mediated transport is inhibited by clofazimine and fidaxomicin [488, 744]. OST$\alpha$ is suggested to be a seven TMprotein, while OST$\beta$ is a single TM 'ancillary' protein, both of which are thought to have intracellular C-termini [458]. Both proteins function in solute transport [132, 458]. Inherited mutations in OST$\alpha$ and OST$\beta$ are associated with liver disease and congenital diarrhea in children [251, 682].

| | | |
|---|---|---|
| Nomenclature | Organic solute transporter subunit $\alpha$ | Organic solute transporter subunit $\beta$ |
| Systematic nomenclature | SLC51A1 | SLC51B |
| Common abbreviation | OST$\alpha$ | OST$\beta$ |
| HGNC, UniProt | *SLC51A*, Q86UW1 | *SLC51B*, Q86UW2 |

**Further reading on SLC51 family of steroid-derived molecule transporters**

Ballatori N. (2011) Pleiotropic functions of the organic solute transporter Ost$\alpha$-Ost$\beta$. *Dig Dis* **29**: 13-7 [PMID:21691099]

Ballatori N *et al.* (2013) The heteromeric organic solute transporter, OST$\alpha$-OST$\beta$/SLC51: a transporter for steroid-derived molecules. *Mol Aspects Med* **34**: 683-92 [PMID:23506901]

Beaudoin JJ *et al.* (2020) Role of Organic Solute Transporter Alpha/Beta in Hepatotoxic Bile Acid Transport and Drug Interactions. *Toxicol Sci* **176**: 34-35 [PMID:32294204]

Dawson PA. (2011) Role of the intestinal bile acid transporters in bile acid and drug disposition. *Handb Exp Pharmacol* 169-203 [PMID:21103970]

Malinen MM *et al.* (2018) Organic solute transporter OST$\alpha$/$\beta$ is overexpressed in nonalcoholic steatohepatitis and modulated by drugs associated with liver injury. *Am J Physiol Gastrointest Liver Physiol* **314**: G597-G609 [PMID:29420067]

# SLC52 family of riboflavin transporters

Transporters → SLC superfamily of solute carriers → SLC52 family of riboflavin transporters

**Overview**: Riboflavin, also known as vitamin B2, is a precursor of the enzyme cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Riboflavin transporters are predicted to possess 10 or 11 TM segments.

| | | | |
|---|---|---|---|
| Nomenclature | solute carrier family 52 member 1 | solute carrier family 52 member 2 | solute carrier family 52 member 3 |
| Systematic nomenclature | SLC52A1 | SLC52A2 | SLC52A3 |
| Common abbreviation | RFVT1 | RFVT2 | RFVT3 |
| HGNC, UniProt | *SLC52A1*, Q9NWF4 | *SLC52A2*, Q9HAB3 | *SLC52A3*, Q9NQ40 |
| Endogenous substrates | riboflavin ($K_m$ $1.3 \times 10^{-3}$M) [824] | riboflavin ($K_m$ $9.8 \times 10^{-4}$M) [824] | riboflavin ($K_m$ $3.3 \times 10^{-4}$M) [824] |
| Stoichiometry | Unknown | Unknown | $H^+$-dependent |

**Comments**: Although expressed elsewhere, RFVT3 is found on the luminal surface of intestinal epithelium and is thought to mediate uptake of dietary riboflavin, while RFVT1 and RFVT2 are thought to allow movement from the epithelium into the blood.

**Further reading on SLC52 family of riboflavin transporters**

Yonezawa A *et al.* (2013) Novel riboflavin transporter family RFVT/SLC52: identification, nomenclature, functional characterization and genetic diseases of RFVT/SLC52. *Mol Aspects Med* **34**: 693-701 [PMID:23506902]

# SLC53 Phosphate carriers

Transporters → SLC superfamily of solute carriers → SLC53 Phosphate carriers

| | |
|---|---|
| Nomenclature | xenotropic and polytropic retrovirus receptor 1 |
| Systematic nomenclature | SLC53A1 |
| HGNC, UniProt | *XPR1*, Q9UBH6 |
| Substrates | Phosphate [267] |
| Comments | XPR1/SLC53A1 is a phosphate carrier which appears to play a role in bone and tooth mineralization. It is ubiquitously expressed [52, 692]. The pathological consequences of defective SLC53A1 expression in the brain [450] and kidney [26] have been reported. |

# SLC54 Mitochondrial pyruvate carriers

Transporters → SLC superfamily of solute carriers → SLC54 Mitochondrial pyruvate carriers

**Overview**: Pyruvate is oxidized to acetyl-CoA by pyruvate dehydrogenase which is localized in the mitochondrial matrix. The mitochondrial pyruvate carrier (MPC) is composed of SLC54 family members (MPC1 and MPC2) [86, 333], which form functional hetero-dimers [708, 709]. The MPC is expressed in the inner mitochondrial membrane and involved in the import of pyruvate into mitochondria [86, 333]. Ubiquitous disruption of either MPC1 or MPC2 expression results in embryonic lethality [752, 761]. Clinically relevant concentrations of the insulin sensitizers, thiazolidinediones, inhibit the MPC [172]. Other clinically relevant inhibitors of the MPC complex are lonidamine [533, 708], quinolone antibacterials [338], entacapone and nitrofurantoin [708].

| | | | |
|---|---|---|---|
| Nomenclature | mitochondrial pyruvate carrier 1 | mitochondrial pyruvate carrier 2 | mitochondrial pyruvate carrier 1 like |
| Systematic nomenclature | SLC54A1 | SLC54A2 | SLC54A3 |
| HGNC, UniProt | *MPC1*, Q9Y5U8 | *MPC2*, O95563 | *MPC1L*, P0DKB6 |
| Substrates | Pyruvate [86, 333] | Pyruvate [86, 333] | Pyruvate [751] |
| Inhibitors | UK-5099 ($pIC_{50}$ 7.3) [314] – Rat, α-Cyano-5-phenyl-2,4-pentadienic acid ($pIC_{50}$ 6.7) [314] – Rat, α-cyanocinnamate ($pIC_{50}$ 6.7) [314] – Rat, mitoglitazone ($pIC_{50}$ 5.9) [172] – Mouse | UK-5099 ($pIC_{50}$ 7.3) [314] – Rat, α-Cyano-5-phenyl-2,4-pentadienic acid ($pIC_{50}$ 6.7) [314] – Rat, α-cyanocinnamate ($pIC_{50}$ 6.7) [314] – Rat, zaprinast ($pIC_{50}$ 6.5) [708], entacapone ($pIC_{50}$ 6.2) [708], mitoglitazone ($pIC_{50}$ 5.9) [172] – Mouse, nitrofurantoin ($pIC_{50}$ 5.5) [708], lonidamine ($pIC_{50}$ 5.3) [708] | entacapone [708], lonidamine [708], nitrofurantoin [708], zaprinast [708] |
| Comments | SLC54A1 is ubiquitously expressed [751]. | SLC54A2 is ubiquitously expressed [751]. The inhibitory potency of UK5099 in human MPC1L/MPC2 proteoliposomes is 53 nM [708]. The potency of mitoglitazone (MSDC-0160) in the same system is 2.7 μM [708]. | SLC54A3 is expressed in testis, postmeiotic spermatids and sperm cells [751]. The MPC1L/MPC2 hetero-dimer binds the same inhibitors/antagonists as the MPC1/MPC2 complex [708]. |

**Comments**: SLC54 family of transporters form hetero-dimers responsible for the accumulation of pyruvate into mitochondria, to link glycolysis with oxidative phosphorylation.

### Further reading on SLC54 Mitochondrial pyruvate carriers


Bader DA *et al*. (2019) Mitochondrial pyruvate import is a metabolic vulnerability in androgen receptor-driven prostate cancer. *Nat Metab* **1**: 70-85 [PMID:31198906]

Harrison SA *et al*. (2020) Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study. *J Hepatol* **72**: 613-626 [PMID:31697972]

McCommis KS *et al*. (2017) Targeting the mitochondrial pyruvate carrier attenuates fibrosis in a mouse model of nonalcoholic steatohepatitis. *Hepatology* **65**: 1543-1556 [PMID:28027586]

Tompkins SC *et al*. (2019) Disrupting Mitochondrial Pyruvate Uptake Directs Glutamine into the TCA Cycle away from Glutathione Synthesis and Impairs Hepatocellular Tumorigenesis. *Cell Rep* **28**: 2608-2619.e6 [PMID:31484072]

Yiew NKH *et al*. (2022) The mitochondrial pyruvate carrier at the crossroads of intermediary metabolism. *Am J Physiol Endocrinol Metab* **323**: E33-E52 [PMID:35635330]

# SLC55 Mitochondrial cation/proton exchangers

Transporters → SLC superfamily of solute carriers → SLC55 Mitochondrial cation/proton exchangers

| | | | |
|---|---|---|---|
| Nomenclature | leucine zipper and EF-hand containing transmembrane protein 1 | leucine zipper and EF-hand containing transmembrane protein 2 | LETM1 domain containing 1 |
| Systematic nomenclature | SLC55A1 | SLC55A2 | SLC55A3 |
| HGNC, UniProt | *LETM1*, O95202 | *LETM2*, Q2VYF4 | *LETMD1*, Q6P1Q0 |
| Transport type | Exchanger/$Ca^{2+}$:$H^+$ [374, 657]<br>Exchanger/$K^+$:$H^+$ [171, 545] | – | – |
| Substrates | $Ca^{2+}$, $K^+$, $H^+$ [171, 545, 546, 859] | – | – |
| Comments | SLC55A1 is ubiquitously expressed [198]. Arguments against SLC55A1's role as a $Ca^{2+}$ transporter are outlined by Zotova *et al.* (2010) [859]. | – | – |

**Comments**: The family of SLC55 mitochondrial transporters appear to regulate ion fluxes and to maintain tubular networks.

# SLC56 Sideroflexins

Transporters → SLC superfamily of solute carriers → SLC56 Sideroflexins

| | | | | | |
|---|---|---|---|---|---|
| Nomenclature | sideroflexin 1 | sideroflexin 2 | sideroflexin 3 | sideroflexin 4 | sideroflexin 5 |
| Systematic nomenclature | SLC56A1 | SLC56A2 | SLC56A3 | SLC56A4 | SLC56A5 |
| HGNC, UniProt | *SFXN1*, Q9H9B4 | *SFXN2*, Q96NB2 | *SFXN3*, Q9BWM7 | – | *SFXN5*, Q8TD22 |
| Comments | Sideroflexin 1 (SFXN1/SLC56A1) was probably falsely identified as a tricarboxylate carrier in the 1993 article by Azzi *et al.* [39], as discussed several years later in [226]. SFXN1 likely transports pyridoxin or another heme precursor or the 5'-aminolevulinate synthase 2 (*ALAS2*; P22557) cofactor [226, 826]. SFXN1 has recently been suggested to be a mitochondrial serine transporter [422]. It is mainly expressed in adult kidney and liver (mouse) [226]. | In mice sideroflexin 2 expression is mainly detected in adult kidney and liver [226]. In human tissues it is detected at highest levels in kidney, liver and pancreas [826]. | Sideroflexin 3 is ubiquitously expressed in mouse tissues [226]. | Sideroflexin 4 is expressed in mouse kidney, brain and heart [226]. The SFXN4a isoform is most highly expressed in human kidney and pancreas, and the SFXN4b isoform is barely detectable in brain [847]. | Sideroflexin 5 is expressed in mouse brain and liver [226]. |

**Comments**: These are a family of incompletely-characterised mitochondrial transporters.

# SLC57 NiPA-like magnesium transporter family

Transporters → SLC superfamily of solute carriers → SLC57 NiPA-like magnesium transporter family

| | | | | |
|---|---|---|---|---|
| Nomenclature | NIPA magnesium transporter 1 | NIPA magnesium transporter 2 | NIPA like domain containing 1 | NIPA like domain containing 3 |
| Systematic nomenclature | SLC57A1 | SLC57A2 | SLC57A3 | SLC57A5 |
| HGNC, UniProt | *NIPA1*, Q7RTP0 | *NIPA2*, Q8N8Q9 | *NIPAL1*, Q6NVV3 | *NIPAL3*, Q6P499 |
| Substrates | $Mg^{2+}$ [282], $Sr^{2+}$, $Fe^{2+}$ and $Co^{2+}$ to a lesser extent [283] | $Mg^{2+}$ [283] | $Mg^{2+}$, $Sr^{2+}$, $Ba^{2+}$, $Fe^{2+}$, $Cu^{2+}$ [283] | – |
| Comments | Human tissue expression: Constitutively expressed at low levels, with significant enrichment in the brain [596]. Mouse tissue expression: Widely expressed, including in the heart, kidney, liver, colon, less in the brain, and not in the small intestine [282]. | – | – | – |

# SLC58 MagT-like magnesium transporter family

Transporters → SLC superfamily of solute carriers → SLC58 MagT-like magnesium transporter family

| | | |
|---|---|---|
| Nomenclature | magnesium transporter 1 | tumor suppressor candidate 3 |
| Systematic nomenclature | SLC58A1 | SLC58A2 |
| HGNC, UniProt | *MAGT1*, Q9H0U3 | *TUSC3*, Q13454 |
| Transport type | Channel-like [591] | – |
| Substrates | $Mg^{2+}$ [286] | $Mg^{2+}$, $Fe^{2+}$, $Cu^{2+}$, $Mn^{2+}$ [283, 591] |
| Comments | Expressed in kidney, colon, heart and liver (the latter only at the mRNA level) [286]; universally expressed [848]. | Expressed in placenta, pancreas, testis, ovary, heart, and prostate [481]. |

# SLC59 Sodium-dependent lysophosphatidylcholine symporter family

Transporters → SLC superfamily of solute carriers → SLC59 Sodium-dependent lysophosphatidylcholine symporter family

| | | |
|---|---|---|
| Nomenclature | MFSD2 lysolipid transporter A, lysophospholipid | MFSD2 lysolipid transporter B, sphingolipid |
| Systematic nomenclature | SLC59A1 | SLC59A2 |
| HGNC, UniProt | *MFSD2A*, Q8NA29 | *MFSD2B*, A6NFX1 |
| Transport type | Co-transporter: LPC:$Na^+$, uptake | – |
| Substrates | LPC (lysophosphatidylcholine) form of DHA (docosahexaenoic acid) [539] | – |
| Comments | MFSD2/SLC59A1 has been suggested to be a sphingosine 1-phosphate transporter in erythropoietic cells [414]. It is expressed in brain, intestine, kidney, liver, lung, mammary gland, and prostate [25]; relatively low expression in BAT (brown adipose tissue), but upregulated during cold-induced thermogenesis [25]. Subcellular locations: plasma membrane [773] and ER [25]. | Expressed in the spleen, lung, testis and subcellularly in the ER [25]. |

# SLC60 Glucose transporters

Transporters → SLC superfamily of solute carriers → SLC60 Glucose transporters

| | | |
|---|---|---|
| Nomenclature | major facilitator superfamily domain containing 4A | major facilitator superfamily domain containing 4B |
| Systematic nomenclature | SLC60A1 | SLC60A2 |
| HGNC, UniProt | *MFSD4A*, Q8N468 | *MFSD4B*, Q5TF39 |
| Transport type | – | Co-transporter/$Na^+$ (1:1) uptake (Rat) [340] |
| Substrates | – | $\alpha$-Me-glucose, D-glucose [340] |
| Inhibitors | – | phloretin [340] – Rat, phlorizin [340] – Rat, urea [534] – Rat |
| Comments | – | Expressed in rat kidney (cortex and medulla), brain, liver and lung [340]. |

# SLC61 Molybdate transporter family

Transporters → SLC superfamily of solute carriers → SLC61 Molybdate transporter family

| | |
|---|---|
| Nomenclature | major facilitator superfamily domain containing 5 |
| Systematic nomenclature | SLC61A1 |
| HGNC, UniProt | *MFSD5*, Q6N075 |
| Substrates | molybdate [711] |
| Comments | MFSD5/SLC61 is a putative 12TM cell-surface protein which appears to allow the accumulation of molybdate, and where the neural expression appears to respond to changes in the diet. It is expressed in cervix, stomach, nerve and skin [711]; ubiquitous but higher in skeletal muscle, olfactory bulb [234]; blood, cortex, hypothalamus, cerebellum and spinal cord (mouse) [574]. |

# SLC62 Pyrophosphate transporters

Transporters → SLC superfamily of solute carriers → SLC62 Pyrophosphate transporters

| | |
|---|---|
| Nomenclature | ANKH inorganic pyrophosphate transport regulator |
| Systematic nomenclature | SLC62A1 |
| HGNC, UniProt | *ANKH*, Q9HCJ1 |
| Substrates | Pyrophosphate [336] |
| Comments | ANKH/SLC62 is a putative 8TM membrane protein, also known as progressive ankylosis protein homolog. Mutations in this protein are associated with bone and joint abnormalities. It is expressed in kidney and bone [105]. |

# SLC63 Sphingosine phosphate transporters

Transporters → SLC superfamily of solute carriers → SLC63 Sphingosine phosphate transporters

**Overview**: The SLC63 family of transporters has roles inside the cell (SLC63A1/SPNS1) or on the cell surface (SLC63A2/SPNS2) in sphingolipid transport.

| | |
|---|---|
| Nomenclature | SPNS lysolipid transporter 1, lysophospholipid |
| Systematic nomenclature | SLC63A1 |
| HGNC, UniProt | *SPNS1*, Q9H2V7 |
| Comments | Expressed in mitochondria [822]. |

# SLC64 Golgi $Ca^{2+}/H^{+}$ exchangers

Transporters → SLC superfamily of solute carriers → SLC64 Golgi $Ca^{2+}/H^{+}$ exchangers

| | |
|---|---|
| Nomenclature | transmembrane protein 165 |
| Systematic nomenclature | SLC64A1 |
| HGNC, UniProt | *TMEM165*, Q9HC07 |
| Transport type | Exchanger/$Ca^{2+}$:$H^{+}$ |
| Substrates | $Ca^{2+}$, $H^{+}$ [161], $Mn^{2+}$ [584, 585] |
| Comments | TMEM165/SLC64 is a putative 6TM intracellular membrane protein. Mutations in the protein are associated with congenital disorder of glycosylation. It has been suggested to be essential for milk production in the mammary gland [670]. TMEM165 deficiency (*via* siRNA knockdown) causes Golgi glycosylation defects in transfected HEK cells [233]. |

# SLC65 NPC-type cholesterol transporters

Transporters → SLC superfamily of solute carriers → SLC65 NPC-type cholesterol transporters

**Overview**: The SLC65 family of intracellular cholesterol transporters are 13TM membrane proteins. NPC1/SLC65A1 is an intracellular cholesterol transporter, which together with NPC2 (Uniprot ID P61916), allows the accumulation into the cytosol of cholesterol acquired from low density lipoproteins.

| | | |
|---|---|---|
| Nomenclature | NPC intracellular cholesterol transporter 1 | NPC1 like intracellular cholesterol transporter 1 |
| Systematic nomenclature | SLC65A1 | SLC65A2 |
| HGNC, UniProt | *NPC1*, O15118 | *NPC1L1*, Q9UHC9 |
| Substrates | Cholesterol [354, 355, 577] | Cholesterol [15] |
| Selective antagonists | – | ezetimibe (Inhibition) ($pK_d$ 6.7) [252] |
| Comments | Expression is ubiquitous [15], with highest levels detected in liver, lung, and pancreas [153]. NPC1 plays a critical role in the regulation of intracellular cholesterol trafficking [106]. Mutations in the NPC1 gene have been identified in patients with the lipid storage disorder Niemann-Pick disease type C1 [72, 106, 290, 816]. | Expressed in small intestine, gallbladder, liver, testis and stomach [15]. |

# SLC66 Lysosomal amino acid transporters

Transporters → SLC superfamily of solute carriers → SLC66 Lysosomal amino acid transporters

**Overview**: This is a family of 5 evolutionarily related proteins. Their structural similarities suggest that they are transporters. Biochemical evidence supports transporter activity for SLC66A1 (LAAT1) and SLC66A4 (CTNS; Cystinosin), primarily exporting amino acids from the lysosome to the cytoplasm. The functions of the 3 remaining members of the family are undetermined.

| | | |
|---|---|---|
| Nomenclature | solute carrier family 66 member 1 | solute carrier family 66 member 2 |
| Systematic nomenclature | SLC66A1 | SLC66A2 |
| HGNC, UniProt | *SLC66A1*, Q6ZP29 | *SLC66A2*, Q8N2U9 |
| Comments | Responsible for lysine and arginine export from lysosomes [463]. Functions as a pH-sensitive uniporter [452]. Transports cysteamine-cysteine mixed disulfide, structurally similar to lysine, which is a chemical intermediate formed during cysteamine therapy of cystinosis [373]. Acts to recruit the C9orf72-SMCR8-WDR41 complex to the cytoplasmic side of the lysosome upon cationic amino acid starvation, as the initiator of the signaling cascade [17, 696]. | – |

| | | | |
|---|---|---|---|
| Nomenclature | solute carrier family 66 member 3 | cystinosin, lysosomal cystine transporter | mannose-P-dolichol utilization defect 1 |
| Systematic nomenclature | SLC66A3 | SLC66A4 | SLC66A5 |
| HGNC, UniProt | *SLC66A3*, Q8N755 | *CTNS*, O60931 | *MPDU1*, O75352 |
| Comments | – | Exports cystine (cysteine disulfide) from the lysosomes into the cytoplasm. Acts as a cystine/$H^+$ symporter at a 1:1 stiochiometry [624]. Loss of function causes the monogenic systemic disease cystinosis [383, 727], characterized by intra-lysosomal cystine accumulation in all body cells and organs [197]. | MPDU1 mutations cause congenital disorder of glycosylation type If (CDG-If) [425, 644]. |

**Further reading on SLC66 Lysosomal amino acid transporters**

Jézégou A *et al.* (2012) Heptahelical protein PQLC2 is a lysosomal cationic amino acid exporter underlying the action of cysteamine in cystinosis therapy. *Proc Natl Acad Sci U S A* **109**: E3434-43 [PMID:23169667]
Kalatzis V *et al.* (2001) Cystinosin, the protein defective in cystinosis, is a H(+)-driven lysosomal cystine transporter. *EMBO J* **20**: 5940-9 [PMID:11689434]
Kandasamy P *et al.* (2018) Amino acid transporters revisited: New views in health and disease. *Trends Biochem Sci* **43**: 752-789 [PMID:30177408]
Liu B *et al.* (2012) LAAT-1 is the lysosomal lysine/arginine transporter that maintains amino acid homeostasis. *Science* **337**: 351-4 [PMID:22822152]
Ruivo R *et al.* (2012) Mechanism of proton/substrate coupling in the heptahelical lysosomal transporter cystinosin. *Proc Natl Acad Sci U S A* **109**: E210-7 [PMID:22232659]

# SLCO family of organic anion transporting polypeptides

Transporters → SLC superfamily of solute carriers → SLCO family of organic anion transporting polypeptides

**Overview**: The SLCO superfamily is comprised of the organic anion transporting polypeptides (OATPs). The 11 human OATPs are divided into 6 families and ten subfamilies based on amino acid identity. These proteins are located on the plasma membrane of cells throughout the body. They have 12 TM domains and intracellular termini, with multiple putative glycosylation sites. OATPs mediate the sodium-independent uptake of a wide range of amphiphilic substrates, including many drugs and toxins. Due to the multispecificity of these proteins, this guide lists classes of substrates and inhibitors for each family member. More comprehensive lists of substrates, inhibitors, and their relative affinities may be found in the review articles listed below.

| | | | | |
|---|---|---|---|---|
| Nomenclature | OATP1A2 | OATP1B1 | OATP1B3 | OATP1C1 |
| Systematic nomenclature | SLCO1A2 | SLCO1B1 | SLCO1B3 | SLCO1C1 |
| HGNC, UniProt | *SLCO1A2*, P46721 | *SLCO1B1*, Q9Y6L6 | *SLCO1B3*, Q9NPD5 | *SLCO1C1*, Q9NYB5 |
| Substrates | antibacterials, anticancer drugs, beta blockers, fluoroquinolones, HIV protease inhibitors, deltorphin II, rosuvastatin, bromsulphthalein, talinolol, microcystin-LR [225], fexofenadine, ouabain | $\beta$-lactam antibacterials, anticancer drugs, HIV protease inhibitors, ACE inhibitors, bile acid derivatives and conjugates, endothelin receptor antagonists, opioids, sartans, statins, rifampicin, bromsulphthalein, fexofenadine, antifungals | $\beta$-lactam antibacterials, anticancer drugs, bile acid derivatives and conjugates, opioids, sartans, statins, erythromycin, rifampicin, bromsulphthalein, amanitin, digoxin, phalloidin, saquinavir, fexofenadine, ouabain | statins, bromsulphthalein |

| | | | | |
|---|---|---|---|---|
| Endogenous substrates | bile acids, steroid conjugates, thyroid hormones, bilirubin, $PGE_2$ | steroid conjugates, thyroid hormones, leukotrienes, bilirubin, bile acids, coproporphyrin I [55], coproporphyrin III [55] | CCK-8 (*CCK*, P06307), bile acids, steroid conjugates, thyroid hormones, $LTC_4$, bilirubin, coproporphyrin I [55], coproporphyrin III [55] | steroid conjugates, thyroid hormones |
| Ligands | – | pravastatin (Binding) | – | – |
| Inhibitors | rifamycin SV ($pK_i$ 5) [757], rifampicin ($pK_i$ 4.3) [757], naringin [43] | cyclosporin A ($pK_i$ 7.3) [217, 393], estrone-3-sulphate ($pIC_{50}$ 7.2) [304], rifampicin ($pK_i$ 6) [393], rifamycin SV ($pK_i$ 5.7) [757], gemfibrozil [543], glycyrrhizin, indocyanine green | cyclosporin A ($pIC_{50}$ 6.1) [393, 729], sildenafil ($pIC_{50}$ 6.1) [729], rifampicin ($pIC_{50}$ 5.8) [393, 729], gemfibrozil, glycyrrhizin, rifamycin SV | DPDPE, probenecid, taurocholic acid |
| Labelled ligands | [$^3$H]BSP, [$^3$H]DPDPE, [$^3$H]estrone-3-sulphate | [$^3$H]estradiol-17$\beta$-glucuronide, [$^3$H]estrone-3-sulphate | [$^3$H]BSP, [$^3$H]CCK-8 (human, mouse, rat), [$^3$H]estradiol-17$\beta$-glucuronide | [$^{125}$I]thyroxine, [$^3$H]BSP, [$^3$H]estrone-3-sulphate |
| Comments | Although rat and mouse OATP1A4 are considered the orthologs of human OATP1A2 we do not cross-link to gene or protein databases for these since in reality there are five genes in rodents that arose through gene duplication in this family and it is not clear which one of these is the "true" ortholog. | Other inhibitors include, fibrates, flavonoids, glitazones and macrolide antibacterials. Estrone-3-sulphate or the drug substrates atorvastatin, pravastatin and rosuvastatin are used as a probe. | Other inhibitors include, HIV protease inhibitors, glitazones and macrolide antibacterials. CCK-8 is used as an OATP1B3-selective probe. | – |

| Nomenclature | OATP2A1 | OATP2B1 | OATP3A1 | OATP4A1 | OATP4C1 |
|---|---|---|---|---|---|
| Systematic nomenclature | SLCO2A1 | SLCO2B1 | SLCO3A1 | SLCO4A1 | SLCO4C1 |
| HGNC, UniProt | *SLCO2A1*, Q92959 | *SLCO2B1*, O94956 | *SLCO3A1*, Q9UIG8 | *SLCO4A1*, Q96BD0 | *SLCO4C1*, Q6ZQN7 |
| Substrates | synthetic prostaglandin derivatives | statins, telmisartan, glibenclamide, amiodarone, bosentan, bromsulphthalein, talinolol, aliskiren, fexofenadine | – | penicillin G | anticancer drugs, cardiac glycosides, dipeptidyl peptidase-4 inhibitors |
| Endogenous substrates | prostaglandins, eicosanoids | $T_4$, dehydroepiandrosterone sulphate, estrone-3-sulphate, coproporphyrin III [55] | BQ123, thyroid hormones, prostaglandins, vasopressin (*AVP*, P01185) | bile acids, steroid conjugates, thyroid hormones, prostaglandins | steroid conjugates, thyroid hormones, cyclic AMP |
| Inhibitors | bromocresol green (Inhibition of $PGF_{2\alpha}$ uptake in PGT-expressing HeLa cells) ($pK_i$ 5.4) [386] – Rat, bromsulphthalein (Inhibition of $PGF_{2\alpha}$ uptake in PGT-expressing HeLa cells) ($pK_i$ 5.2) [386] – Rat | erlotinib ($pK_i$ 6.3) [393], verlukast ($pK_i$ 5.6) [393], gemfibrozil, glibenclamide, rifamycin SV, sildenafil [729] | – | – | – |
| Labelled ligands | [$^3$H]$PGE_2$ (Binding) [111] | [$^3$H]BSP, [$^3$H]estrone-3-sulphate | [$^3$H]$PGE_2$, [$^3$H]estrone-3-sulphate | [$^3$H]estrone-3-sulphate | [$^3$H]digoxin |
| Comments | Other inhibitors include NSAIDs | Other inhibitors include glitazones and citrus juices | – | – | – |

### Further reading on SLCO family of organic anion transporting polypeptides

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