THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: TRANSPORTERS

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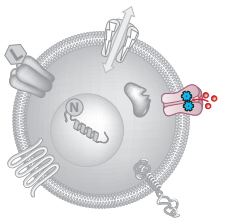

Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

Transporters are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone 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. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An Introduction to Transporters

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 not only 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 52 families of almost 400 members. Many of these 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. Some SLC family members remain orphan transporters, in as much as a physiological function has yet to be determined. 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 movement 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 express enzymatic function. Many of the transporters also express electrogenic properties of ion channels.

Acknowledgements

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Conflict of interest

The authors state that there is no conflict of interest to disclose.

List of records presented

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

Systematic nomenclature	Common abbreviation	HGNC, UniProt	Comment
ABCA1	ABC1, CERP	*ABCA1*, O95477	Loss-of-function mutations are associated with Tangier disease, in which plasma HDL cholesterol levels are greatly reduced
ABCA2	ABC2	*ABCA2*, Q9BZC7	–
ABCA3	ABC3, ABCC	*ABCA3*, Q99758	Loss-of-function mutations are associated with pulmonary surfactant deficiency
ABCA4	ABCR	*ABCA4*, P78363	Retinal-specific transporter of N-retinylPE; loss-of-function mutations are associated with Stargardt disease, a juvenile onset macular degenerative disease
ABCA5	–	*ABCA5*, Q8WWZ7	–
ABCA6	–	*ABCA6*, Q8N139	–
ABCA7	–	*ABCA7*, Q8IZY2	Genome wide association studies identify ABCA7 variants as associated with Alzheimer's Disease [6]
ABCA8	–	*ABCA8*, O94911	–
ABCA9	–	*ABCA9*, Q8IUA7	–
ABCA10	–	*ABCA10*, Q8WWZ4	–
ABCA12	–	*ABCA12*, Q86UK0	Reported to play a role in skin ceramide formation [23]
ABCA13	–	*ABCA13*, Q86UQ4	–

Comments: A number of structural analogues are not found in man: ABCA14 (ENSMUSG00000062017); ABCA15 (ENSMUSG00000054746); ABCA16 (ENSMUSG00000051900) and ABCA17 (ENSMUSG00000035435).

ABCB subfamily

Systematic nomenclature	Common abbreviation	HGNC, UniProt	Comment
ABCB1	MDR1, PGP1	*ABCB1*, P08183	Responsible for the cellular export of many therapeutic drugs. The mouse and rat have two Mdr1 genes (gene names; Mdr1a and Mdr1b) while the human has only the one gene, MDR1
ABCB2	TAP1	*TAP1*, Q03518	Endoplasmic reticulum peptide transporter, possibly requires heterodimerization with TAP2
ABCB3	TAP2	*TAP2*, Q03519	Endoplasmic reticulum peptide transporter, possibly requires heterodimerization with TAP1
ABCB4	PGY3	*ABCB4*, P21439	Transports phosphatidylcholine from intracellular to extracellular face of the hepatocyte canalicular membrane [13]
ABCB5	–	*ABCB5*, Q2M3G0	Multidrug resistance protein in, and marker of, melanoma cells [17]
ABCB6	MTABC3	*ABCB6*, Q9NP58	Putative mitochondrial porphyrin transporter [11]; other subcellular localizations are possible, such as the plasma membrane, as a specific determinant of the Langereis blood group system [5]
ABCB7	ABC7	*ABCB7*, O75027	Mitochondrial; reportedly essential for haematopoiesis [15]
ABCB8	MABC1	*ABCB8*, Q9NUT2	Mitochondrial; suggested to play a role in chemoresistance of melanoma [4]
ABCB9	TAPL	*ABCB9*, Q9NP78	Reported to be lysosomal [7]
ABCB10	MTABC2	*ABCB10*, Q9NRK6	Mitochondrial location; the first human ABC transporter to have a crystal structure reported [18]
ABCB11	ABC16	*ABCB11*, O95342	Loss-of-function mutations are associated with progressive familial intrahepatic cholestasis type 2 [19]

ABCC subfamily

Systematic nomenclature	Common abbreviation	HGNC, UniProt	Comment
ABCC1	MRP1	*ABCC1*, P33527	Exhibits a broad substrate specificity [1], including LTC_4 (K_m 97 nM [12]) and estradiol-17β-glucuronide [20]
ABCC2	MRP2, cMOAT	*ABCC2*, Q92887	Loss-of-function mutations are associated with Dubin-Johnson syndrome, in which plasma levels of conjugated bilirubin are elevated (OMIM: 237500)
ABCC3	MRP3	*ABCC3*, O15438	Transports conjugates of glutathione, sulfate or glucuronide [2]
ABCC4	MRP4	*ABCC4*, O15439	Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned [2]; reported to export prostaglandins in a manner sensitive to NSAIDS [16]
ABCC5	MRP5	*ABCC5*, O15440	Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned [2]
ABCC6	MRP6	*ABCC6*, O95255	Loss-of-function mutations in ABCC6 are associated with pseudoxanthoma elasticum (OMIM: 264800)
ABCC10	MRP7	*ABCC10*, Q5T3U5	–
ABCC11	MRP8	*ABCC11*, Q96J66	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
ABCC12	MRP9	*ABCC12*, Q96J65	–

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

Overview: This family of 'half-transporters' act as homo- or heterodimers to accumulate fatty acid-CoA esters into peroxisomes for oxidative metabolism [9].

Systematic nomenclature	Common abbreviation	HGNC, UniProt	Comment
ABCD1	ALDP	*ABCD1*, P33897	Transports coenzyme A esters of very long chain fatty acids [21–22]; loss-of-function mutations in ABCD1 are associated with adrenoleukodystrophy (OMIM: 3001002)
ABCD2	ALDR	*ABCD2*, Q9UBJ2	Coenzyme A esters of very long chain unsaturated fatty acids [22]
ABCD3	PMP70	*ABCD3*, P28288	–

Comments: ABCD4 (ENSG00000119688, also known as PMP69, PXMP1-L or P70R) appears to be located on the endoplasmic reticulum [8], with an unclear function. Loss-of-function mutations in the gene encoding ALDP underlie the metabolic storage disorder X-linked adrenoleukodystrophy.

ABCG subfamily

Overview: This family of 'half-transporters' act as homo- or heterodimers; particularly ABCG5 and ABCG8 are thought to be obligate heterodimers. They are associated with cellular export of sterols and phospholipids, as well as exogenous drugs (ABCG2).

Systematic nomenclature	Common abbreviation	HGNC, UniProt	Comment
ABCG1	ABC8	*ABCG1*, P45844	Transports sterols and choline phospholipids [10]
ABCG2	ABCP	*ABCG2*, Q9UNQ0	Exhibits a broad substrate specificity, including urate and haem, as well as multiple synthetic compounds [10]. The functional transporter is likely to be a homodimer, although higher oligomeric states have also been proposed
ABCG4	–	*ABCG4*, Q9H172	Putative functional dependence on ABCG1
ABCG5	–	*ABCG5*, Q9H222	Transports phytosterols and cholesterol; forms an obligate heterodimer with ABCG8. Loss-of-function mutations in ABCG5 are associated with sitosterolemia (OMIM: 210250)
ABCG8	–	*ABCG8*, Q9H221	Transports phytosterols and cholesterol; forms an obligate heterodimer with ABCG5. Loss-of-function mutations in ABCG8 are associated with sitosterolemia (OMIM: 210250)

Comments: 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 [3,14]: 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

Aye IL, Singh AT, Keelan JA. (2009) Transport of lipids by ABC proteins: interactions and implications for cellular toxicity, viability and function. *Chem Biol Interact* **180**: 327–339. [PMID:19426719]

Gutmann DA, Ward A, Urbatsch IL, Chang G, van Veen HW. (2010) Understanding polyspecificity of multidrug ABC transporters: closing in on the gaps in ABCB1. *Trends Biochem Sci* **35**: 36–42. [PMID:19819701]

Hinz A, Tampé R. (2012) ABC transporters and immunity: mechanism of self-defense. *Biochemistry* **51**: 4981–4989. [PMID:22668350]

Kemp S, Theodoulou FL, Wanders RJ. (2011) Mammalian peroxisomal ABC transporters: from endogenous substrates to pathology and clinical significance. *Br J Pharmacol* **164**: 1753–1766. [PMID:21488864]

Kerr ID, Haider AJ, Gelissen IC. (2011) The ABCG family of membrane-associated transporters: you don't have to be big to be mighty. *Br J Pharmacol* **164**: 1767–1779. [PMID:21175590]

Miller DS. (2010) Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. *Trends Pharmacol Sci* **31**: 246–254. [PMID:20417575]

Procko E, O'Mara ML, Bennett WF, Tieleman DP, Gaudet R. (2009) The mechanism of ABC transporters: general lessons from structural and functional studies of an antigenic peptide transporter. *FASEB J* **23**: 1287–1302. [PMID:19174475]

Ravna AW, Sager G. (2009) Molecular modeling studies of ABC transporters involved in multidrug resistance. *Mini Rev Med Chem* **9**: 186–193. [PMID:19200023]

Rees DC, Johnson E, Lewinson O. (2009) ABC transporters: the power to change. *Nat Rev Mol Cell Biol* **10**: 218–227. [PMID:19234479]

Seeger MA, van Veen HW. (2009) Molecular basis of multidrug transport by ABC transporters. *Biochim Biophys Acta* **1794**: 725–737. [PMID:19135557]

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

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 $\alpha 3\beta 3\gamma\delta\varepsilon$.

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.

Nomenclature	α subunit	β subunit	γ subunit	δ subunit	ε subunit
HGNC, UniProt	*ATP5A1*, P25705	*ATP5B*, P06576	*ATP5C1*, P36542	*ATP5D*, P30049	*ATP5E*, P56381

Nomenclature	A subunit	B subunit	C subunit	D subunit	E subunit	F2 subunit	F6 subunit	G2 subunit	8 subunit
HGNC, UniProt	*MT-ATP6*, P00846	*ATP5F1*, P24539	*ATP5G1*, P05496; *ATP5G2*, P48201; *ATP5G3*, Q06055	*ATP5H*, O75947	*ATP5I*, P56385	*ATP5J2*, P56134	*ATP5J*, P18859	*ATP5L2*, Q7Z4Y8	*MT-ATP8*, P03928

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

Nomenclature	A subunit	B1 subunit	B2 subunit	C1 subunit	C2 subunit	D subunit	E1 subunit	E2 subunit	F subunit	G1 subunit	G2 subunit	G3 subunit	H subunit
HGNC, UniProt	*ATP6V1A*, P38606	*ATP6V1B1*, P15313	*ATP6V1B2*, P21281	*ATP6V1C1*, P21283	*ATP6V1C2*, Q8NEY4	*ATP6V1D*, Q9Y5K8	*ATP6V1E1*, P36543	*ATP6V1E2*, Q96A05	*ATP6V1F*, Q16864	*ATP6V1G1*, O75348	*ATP6V1G2*, O95670	*ATP6V1G3*, Q96LB4	*ATP6V1H*, Q9UI12

Nomenclature	a1 subunit	a2 subunit	a3 subunit	a4 subunit	b subunit	c subunit	d1 subunit	d2 subunit	e1 subunit	e2 subunit
HGNC, UniProt	*ATP6V0A1*, Q93050	*ATP6V0A2*, Q9Y487	*TCIRG1*, Q13488	*ATP6V0A4*, Q9HBG4	*ATP6V0B*, Q99437	*ATP6V0C*, P27449	*ATP6V0D1*, P61421	*ATP6V0D2*, Q8N8Y2	*ATP6V0E1*, O15342	*ATP6V0E2*, Q8NHE4

Further reading

El Far O, Seagar M. (2011) A role for V-ATPase subunits in synaptic vesicle fusion?. *J Neurochem* **117**: 603–612. [PMID:21375531]

Junge W, Sielaff H, Engelbrecht S. (2009) Torque generation and elastic power transmission in the rotary F(O)F(1)-ATPase. *Nature* **459**: 364–370. [PMID:19458712]

Mindell JA. (2012) Lysosomal acidification mechanisms. *Annu Rev Physiol* **74**: 69–86. [PMID:22335796]

Nakamoto RK, Baylis Scanlon JA, Al-Shawi MK. (2008) The rotary mechanism of the ATP synthase. *Arch Biochem Biophys* **476**: 43–50. [PMID:18515057]

Nakanishi-Matsui M, Sekiya M, Nakamoto RK, Futai M. (2010) The mechanism of rotating proton pumping ATPases. *Biochim Biophys Acta* **1797**: 1343–1352. [PMID:20170625]

Okuno D, Iino R, Noji H. (2011) Rotation and structure of FoF1-ATP synthase. *J Biochem* **149**: 655–664. [PMID:21524994]

von Ballmoos C, Cook GM, Dimroth P. (2008) Unique rotary ATP synthase and its biological diversity. *Annu Rev Biophys* **37**: 43–64. [PMID:18573072]

von Ballmoos C, Wiedenmann A, Dimroth P. (2009) Essentials for ATP synthesis by F1F0 ATP synthases. *Annu Rev Biochem* **78**: 649–672. [PMID:19489730]

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.

Na^+/K^+-ATPases (EC 3.6.3.9)

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 α subunits and one of three smaller, single TM domain glycoprotein β-subunits (see table). Additional protein partners known as FXYD proteins (*e.g.* FXYD2, P54710) appear to associate with and regulate the activity of the pump.

Nomenclature	α1 subunit	α2 subunit	α3 subunit	α4 subunit	β1 subunit	β2 subunit	β3 subunit
HGNC, UniProt	*ATP1A1*, P05023	*ATP1A2*, P50993	*ATP1A3*, P13637	*ATP1A4*, Q13733	*ATP1B1*, P05026	*ATP1B2*, P14415	*ATP1B3*, P54709

Comments: Na^+/K^+-ATPases are inhibited by ouabain and cardiac glycosides, such as digoxin, as well as potentially endogenous cardiotonic steroids [24].

Ca^{2+}-ATPases (EC 3.6.3.8)

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.

Nomenclature	SERCA1	SERCA2	SERCA3
HGNC, UniProt	*ATP2A1*, O14983	*ATP2A2*, P16615	*ATP2A3*, Q93084

Comments: The fungal toxin ochratoxin A has been described to activate SERCA in kidney microsomes [25]. cyclopiazonic acid [29], thapsigargin [27] and BHQ are widely employed to block SERCA. Thapsigargin has also been described to block the TRPV1 vanilloid receptor [30].

Nomenclature	PMCA1	PMCA2	PMCA3	PMCA4
HGNC, UniProt	*ATP2B1*, P20020	*ATP2B2*, Q01814	*ATP2B3*, Q16720	*ATP2B4*, P23634

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

Nomenclature	SPCA1	SPCA2
HGNC, UniProt	*ATP2C1*, P98194	*ATP2C2*, O75185

Comments: Loss-of-function mutations in SPCA1 appear to underlie Hailey-Hailey disease [26].

H^+/K^+-ATPases (EC 3.6.3.10)

Overview: The H^+/K^+ ATPase is a heterodimeric protein, made up of α and β subunits. The α subunit has 10 TM domains and exhibits catalytic and pore functions, while the β subunit has a single TM domain, which appears to be required for intracellular trafficking and stabilising the α subunit. The ATP4A and ATP4B subunits are expressed together, while the ATP12A subunit is suggested to be expressed with the β1 (ATP1B1) subunit of the Na^+/K^+-ATPase [28].

Nomenclature	ATP4A	ATP12A	ATP4B
HGNC, UniProt	*ATP4A*, P20648	*ATP12A*, P54707	*ATP4B*, P51164

Comments: The gastric H^+/K^+-ATPase is inhibited by proton pump inhibitors used for treating excessive gastric acid secretion, including (R)-lansoprazole and a metabolite of esomeprazole.

Cu^+-ATPases (EC 3.6.3.4)

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).

Nomenclature	ATP7A	ATP7B
HGNC, UniProt	*ATP7A*, Q04656	*ATP7B*, P35670

Phospholipid-transporting ATPases (EC 3.6.3.1)

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.

Nomenclature	ATP8A1	ATP8A2	ATP8B1	ATP8B2	ATP8B3	ATP8B4	ATP9A	ATP9B	ATP10A	ATP10B	ATP10D	ATP11A	ATP11B	ATP11C
HGNC, UniProt	*ATP8A1*, Q9Y2Q0	*ATP8A2*, Q9NTI2	*ATP8B1*, O43520	*ATP8B2*, P98198	*ATP8B3*, O60423	*ATP8B4*, Q8TF62	*ATP9A*, O75110	*ATP9B*, O43861	*ATP10A*, O60312	*ATP10B*, O94823	*ATP10D*, Q9P241	*ATP11A*, P98196	*ATP11B*, Q9Y2G3	*ATP11C*, Q8NB49

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

A further series of structurally-related proteins have been identified in the human genome, with as yet undefined function, including ATP13A1 (Q9HD20), ATP13A2 (Q9NQ11), ATP13A3 (Q9H7F0), ATP13A4 (Q4VNC1) and ATP13A5 (Q4VNC0).

Further reading

Argüello JM, Raimunda D, González-Guerrero M. (2012) Metal transport across biomembranes: emerging models for a distinct chemistry. *J Biol Chem* **287**: 13510–13517. [PMID:22389499]

Benarroch EE. (2011) Na+, K+-ATPase: functions in the nervous system and involvement in neurologic disease. *Neurology* **76**: 287–293. [PMID:21242497]

Brini M, Carafoli E. (2009) Calcium pumps in health and disease. *Physiol Rev* **89**: 1341–1378. [PMID:19789383]

Bublitz M, Musgaard M, Poulsen H, Thøgersen L, Olesen C, Schiøtt B, Morth JP, Møller JV, Nissen P. (2013) Ion pathways in the sarcoplasmic reticulum Ca2+-ATPase. *J Biol Chem* **288**: 10759–10765. [PMID:23400778]

Cereijido M, Contreras RG, Shoshani L, Larre I. (2012) The Na+-K+-ATPase as self-adhesion molecule and hormone receptor. *Am J Physiol, Cell Physiol* **302**: C473–C481. [PMID:22049208]

Galougahi KK, Liu CC, Bundgaard H, Rasmussen HH. (2012) β-Adrenergic regulation of the cardiac Na+-K+ ATPase mediated by oxidative signaling. *Trends Cardiovasc Med* **22**: 83–87. [PMID:23040838]

Gupta SP. (2012) Quantitative structure-activity relationship studies on Na+,K(+)-ATPase inhibitors. *Chem Rev* **112**: 3171–3192. [PMID:22360614]

Kaler SG. (2011) ATP7A-related copper transport diseases-emerging concepts and future trends. *Nat Rev Neurol* **7**: 15–29. [PMID:21221114]

López-Marqués RL, Holthuis JC, Pomorski TG. (2011) Pumping lipids with P4-ATPases. *Biol Chem* **392**: 67–76. [PMID:21194369]

Mattle D, Sitsel O, Autzen HE, Meloni G, Gourdon P, Nissen P. (2013) On allosteric modulation of P-type Cu(+)-ATPases. *J Mol Biol* **425**: 2299–2308. [PMID:23500486]

Michelangeli F, East JM. (2011) A diversity of SERCA Ca2+ pump inhibitors. *Biochem Soc Trans* **39**: 789–797. [PMID:21599650]

Morth JP, Pedersen BP, Buch-Pedersen MJ, Andersen JP, Vilsen B, Palmgren MG, Nissen P. (2011) A structural overview of the plasma membrane Na+,K+-ATPase and H+-ATPase ion pumps. *Nat Rev Mol Cell Biol* **12**: 60–70. [PMID:21179061]

Palmgren MG, Nissen P. (2011) P-type ATPases. *Annu Rev Biophys* **40**: 243–266. [PMID:21351879]

Pittman JK. (2011) Vacuolar Ca(2+) uptake. *Cell Calcium* **50**: 139–146. [PMID:21310481]

Pizzo P, Lissandron V, Capitanio P, Pozzan T. (2011) Ca(2+) signalling in the Golgi apparatus. *Cell Calcium* **50**: 184–192. [PMID:21316101]

Reinhard L, Tidow H, Clausen MJ, Nissen P. (2013) Na(+),K (+)-ATPase as a docking station: protein-protein complexes of the Na(+),K (+)-ATPase. *Cell Mol Life Sci* **70**: 205–222. [PMID:22695678]

Sebastian TT, Baldridge RD, Xu P, Graham TR. (2012) Phospholipid flippases: building asymmetric membranes and transport vesicles. *Biochim Biophys Acta* **1821**: 1068–1077. [PMID:22234261]

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 [31,37,64–65,76].

Glutamate transporter subfamily

Overview: Glutamate transporters present the unusual structural motif of 8TM segments and 2 re-entrant loops [60]. 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 [38,78,93] reviewed by [63]). This structural data is in agreement with the proposed quaternary structure for EAAT2 [55] and several functional studies that propose the monomer is the functional unit [57,67,69,83]. Recent evidence suggests that EAAT3 and EAAT4 may assemble as heterotrimers [74]. 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 [80]. Recent evidence supports altered glutamate transport and novel roles in brain for splice variants of EAAT1 and EAAT2 [54,70]. Three patients with dicarboxylic aminoaciduria (DA) were recently found to have loss-of-function mutations in EAAT3 [36]. 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 β-lactam antibiotics (*e.g.* ceftriaxone) is neuroprotective and occurs through NF-κB-mediated EAAT2 promoter activation [53,71,81] reviewed by [66]). PPARγ activation (*e.g.* by rosiglitazone) also leads to enhanced expression of EAAT though promoter activation [79]. In addition, several translational activators of EAAT2 have recently been described [42] along with treatments that increase the surface expression of EAAT2 (*e.g.* [68]; [98]), or prevent its down-regulation (*e.g.* [56]). A thermodynamically uncoupled Cl^- flux, activated by Na^+ and glutamate [59,64,73] (Na^+ and aspartate in the case of GltPh [82]), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability [88,92]. 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 [52].

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
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid, L-cysteine [94]	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid
Substrates	DL-threo-β-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid	DL-threo-β-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid	DL-threo-β-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid	DL-threo-β-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid	DL-threo-β-hydroxyaspartate, L-trans-2,4-pyrolidine dicarboxylate, D-aspartic acid
Inhibitors (pIC_{50})	DL-TBOA (pK_B 5.0) [85], UCPH-101 (membrane potential assay) (6.9) [62]	DL-TBOA (pK_B 6.9) [85], SYM2081 (pK_B 5.5) [91], dihydrokainate (pK_B 5.0), threo-3-methylglutamate (pK_B 4.7) [91], WAY-213613 (6.9)	NBI-59159 (7.6), L-β-BA ([^{3}H]D-aspartate uptake assay) (6.1), DL-TBOA (5.1)	DL-TBOA (pK_i 5.4) [84], threo-3-methylglutamate (pK_i 4.3) [47]	DL-TBOA (pK_i 5.5) [84]
Radioligands (K_d)	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]D-aspartic acid, [^{3}H]L-aspartic acid, [^{3}H]ETB-TBOA ($1.55x10^{-8}$ M)	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]D-aspartic acid, [^{3}H]L-aspartic acid, [^{3}H]ETB-TBOA ($1.62x10^{-8}$ M)	[^{3}H]D-aspartic acid, [^{3}H]L-aspartic acid, [^{3}H]ETB-TBOA ($3.2x10^{-7}$ M)	[^{3}H]D-aspartic acid, [^{3}H]L-aspartic acid, [^{3}H]ETB-TBOA ($2.48x10^{-8}$ M)	[^{3}H]D-aspartic acid, [^{3}H]L-aspartic acid, [^{3}H]ETB-TBOA ($2.95x10^{-8}$ M)
Stoichiometry	Probably 3 Na^+: 1 H^+ : 1 glutamate (in): 1 K^+ (out)	3 Na^+: 1 H^+ : 1 glutamate (in): 1 K^+ (out) [72]	3 Na^+: 1 H^+ : 1 glutamate (in): 1 K^+ (out) [95]	Probably 3 Na^+: 1 H^+ : 1 glutamate (in): 1 K^+(out)	Probably 3 Na^+: 1 H^+ : 1 glutamate (in): 1 K^+ (out)

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 [47,84–85,91]. K_B (or K_i) values derived in uptake assays are generally higher (*e.g.* [85]). 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 = 54μM; [61,91]) and additionally is a potent kainate receptor agonist [97] which renders the compound unsuitable for autoradiographic localisation of EAATs [33]. Similarly, at concentrations that inhibit EAAT2, dihydrokainate binds to kainate receptors [85]. WAY-855 and WAY-213613 are both non-substrate inhibitors with a preference for EAAT2 over EAAT3 and EAAT1 [45–46]. NBI-59159 is a non-substrate inhibitor with modest selectivity for EAAT3 over EAAT1 (>10-fold) and EAAT2 (5-fold) [43–44]. Analogously, L-β-*threo*-benzyl-aspartate (L-β-BA) is a competitive non-substrate inhibitor that preferentially blocks EAAT3 versus EAAT1, or EAAT2 [48]. [^{3}H](2S,4R)-4-methylglutamate demonstrates low affinity binding ($K_D \cong 6.0$ μM) to EAAT1 and EAAT2 in rat brain homogenates [34] and EAAT1 in murine astrocyte membranes [32], whereas [^{3}H]ETB-TBOA binds with high affinity to all EAATs other than EAAT3 [86]. The novel isoxazole derivative (–)-HIP-A may interact at the same site as TBOA and preferentially inhibit reverse transport of glutamate [41]. 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 [47]. 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 [50–51]. In addition to the agents listed in the table, DL-threo-β-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 [90]).

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 [35,89]. ASCT1 and ASCT2 also exhibit thermodynamically uncoupled chloride channel activity associated with substrate transport [40,96]. Whereas EAATs counter-transport K^+ (see above) ASCTs do not and their function is independent of the intracellular concentration of K^+ [96].

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)
Inhibitors (pIC_{50})	–	benzylcysteine [58], benzylserine [58], p-nitrophenyl glutamyl anilide [49]
Stoichiometry	1 Na^+: 1 amino acid (in): 1 Na^+: 1 amino acid (out); (homo-, or hetero-exchange; [95])	1 Na^+: 1 amino acid (in): 1 Na^+: 1 amino acid (out); (homo-, or hetero-exchange; [39])

Comments: The substrate specificity of ASCT1 may extend to L-proline and L-hydroxyproline [77]. At low pH (~5.5) both ASCT1 and ASCT2 are able to exchange acidic amino acids such as L-cysteate and glutamate [87,89]. In addition to the inhibitors tabulated above, $HgCl_2$, methylmercury, mersalyl, at low micromolar concentrations, non-competitively inhibit ASCT2 by covalent modificiation of cysteine residues [75].

Further reading

Bröer S, Palacín M. (2011) The role of amino acid transporters in inherited and acquired diseases. *Biochem J* **436**: 193–211. [PMID:21568940]

Chao XD, Fei F, Fei Z. (2010) The role of excitatory amino acid transporters in cerebral ischemia. *Neurochem Res* **35**: 1224–1230. [PMID:20440555]

Jiang J, Amara SG. (2011) New views of glutamate transporter structure and function: advances and challenges. *Neuropharmacology* **60**: 172–181. [PMID:20708631]

Kanai Y, Clémençon B, Simonin A, Leuenberger M, Lochner M, Weisstanner M, Hediger MA. (2013) The SLC1 high-affinity glutamate and neutral amino acid transporter family. *Mol Aspects Med* **34**: 108–120. [PMID:23506861]

Kim K, Lee SG, Kegelman TP, Su ZZ, Das SK, Dash R, Dasgupta S, Barral PM, Hedvat M, Diaz P et al. (2011) Role of excitatory amino acid transporter-2 (EAAT2) and glutamate in neurodegeneration: opportunities for developing novel therapeutics. *J Cell Physiol* **226**: 2484–2493. [PMID:21792905]

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

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 [105].

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	D-glucose = D-glucosamine [104], dehydroascorbic acid [99]	D-glucosamine > D-glucose [104]	D-glucose	D-glucosamine ≥ D-glucose [104]	–
Radioligands (K_d)	[^{3}H]2-deoxyglucose	[^{3}H]2-deoxyglucose	[^{3}H]2-deoxyglucose	[^{3}H]2-deoxyglucose	–

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 6	Glucose transporter 8	Glucose transporter 10	Glucose transporter 12
Systematic nomenclature	SLC2A6	SLC2A8	SLC2A10	SLC2A12
Common abbreviation	GLUT6	GLUT8	GLUT10	GLUT12
HGNC, UniProt	*SLC2A6*, Q9UGQ3	*SLC2A8*, Q9NY64	*SLC2A10*, O95528	*SLC2A12*, Q8TD20
Substrates	–	D-glucose [101]	D-glucose [102], dehydroascorbic acid [102]	D-glucose [103]

Proton-coupled inositol transporter

Overview: Proton-coupled inositol transporters are expressed predominantly in the brain and can be inhibited by phloretin and cytochalasin B [104].

Nomenclature	Proton *myo*-inositol cotransporter
Systematic nomenclature	SLC2A13
Common abbreviation	HMIT
HGNC, UniProt	*SLC2A13*, Q96QE2
Substrates	*myo*-inositol [104], D-*chiro*-inositol [104], *muco*-inositol [104], *scyllo*-inositol [104]
Stoichiometry	1 H^+ : 1 inositol (in) [100]

Further reading

Augustin R. (2010) The protein family of glucose transport facilitators: It's not only about glucose after all. *IUBMB Life* **62**: 315–333. [PMID:20209635]

Leney SE, Tavaré JM. (2009) The molecular basis of insulin-stimulated glucose uptake: signalling, trafficking and potential drug targets. *J Endocrinol* **203**: 1–18. [PMID:19389739]

Mueckler M, Thorens B. (2013) The SLC2 (GLUT) family of membrane transporters. *Mol Aspects Med* **34**: 121–138. [PMID:23506862]

Uldry M, Thorens B. (2004) The SLC2 family of facilitated hexose and polyol transporters. *Pflugers Arch* **447**: 480–489. [PMID:12750891]

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).

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.

Nomenclature	rBAT	4F2hc
Systematic nomenclature	SLC3A1	SLC3A2
Common abbreviation	rBAT	4F2hc
HGNC, UniProt	*SLC3A1*, Q07837	*SLC3A2*, P08195

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	Cationic amino acid transporter 4	Probable cationic amino acid transporter
Systematic nomenclature	SLC7A1	SLC7A2	SLC7A3	SLC7A4	SLC7A14
Common abbreviation	CAT1	CAT2	CAT3	CAT4	–
HGNC, UniProt	*SLC7A1*, P30825	*SLC7A2*, P52569	*SLC7A3*, Q8WY07	*SLC7A4*, O43246	*SLC7A14*, Q8TBB6
Substrates	L-arginine, L-lysine, L-ornithine, L-histidine	L-arginine, L-lysine, L-ornithine, L-histidine	L-arginine, L-lysine, L-ornithine	–	–

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.

Nomenclature	L-type amino acid transporter 1	L-type amino acid transporter 2	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
Systematic nomenclature	SLC7A5	SLC7A8	SLC7A7	SLC7A6	SLC7A9	SLC7A10	SLC7A11
Common abbreviation	LAT1	LAT2	y+LAT1	y+LAT2	$b^{0,+}$AT	Asc-1	xCT
HGNC, UniProt	*SLC7A5*, Q01650	*SLC7A8*, Q9UHI5	*SLC7A7*, Q9UM01	*SLC7A6*, Q92536	*SLC7A9*, P82251	*SLC7A10*, Q9NS82	*SLC7A11*, Q9UPY5

Comments: CAT4 appears to be non-functional in heterologous expression [106], while SLC7A14 has yet to be characterized.

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

Closs EI, Boissel JP, Habermeier A, Rotmann A. (2006) Structure and function of cationic amino acid transporters (CATs). *J Membr Biol* **213**: 67–77. [PMID:17417706]

Fotiadis D, Kanai Y, Palacín M. (2013) The SLC3 and SLC7 families of amino acid transporters. *Mol Aspects Med* **34**: 139–158. [PMID:23506863]

Palacín M, Kanai Y. (2004) The ancillary proteins of HATs: SLC3 family of amino acid transporters. *Pflugers Arch* **447**: 490–494. [PMID:14770309]

Palacín M, Nunes V, Font-Llitjós M, Jiménez-Vidal M, Fort J, Gasol E, Pineda M, Feliubadaló L, Chillarón J, Zorzano A. (2005) The genetics of heteromeric amino acid transporters. *Physiology (Bethesda)* **20**: 112–124. [PMID:15772300]

Verrey F, Closs EI, Wagner CA, Palacin M, Endou H, Kanai Y. (2004) CATs and HATs: the SLC7 family of amino acid transporters. *Pflugers Arch* **447**: 532–542. [PMID:14770310]

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

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

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^+ : 2HCO_3^- (in) : 1 Cl^- (out)	–

Further reading

Alper SL. (2009) Molecular physiology and genetics of Na+-independent SLC4 anion exchangers. *J Exp Biol* **212** (Pt 11): 1672–1683. [PMID:19448077]

Boron WF, Chen L, Parker MD. (2009) Modular structure of sodium-coupled bicarbonate transporters. *J Exp Biol* **212** (Pt 11): 1697–1706. [PMID:19448079]

Liu Y, Wang DK, Chen LM. (2012) The physiology of bicarbonate transporters in mammalian reproduction. *Biol Reprod* **86**: 99. [PMID:22262691]

Majumdar D, Bevensee MO. (2010) Na-coupled bicarbonate transporters of the solute carrier 4 family in the nervous system: function, localization, and relevance to neurologic function. *Neuroscience* **171**: 951–972. [PMID:20884330]

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

Romero MF, Chen AP, Parker MD, Boron WF. (2013) The SLC4 family of bicarbonate (HCO_3^-) transporters. *Mol Aspects Med* **34**: 159–182. [PMID:23506864]

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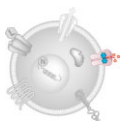
Full Contents of Concise Guide: http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full



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^- [121-122,142-143]. 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 α-helical domains [107].

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 [142] 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 [117].

Nomenclature	SGLT1	SGLT2	SGLT3	SGLT4	SGLT5
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, α-MDG, D-galactose	D-glucose, α-MDG	D-glucose, N-ethyl-1-deoxynojirimycin, 1-deoxynojirimycin, 1-deoxynojirimycin-1-sulfonic acid, miglustat, miglitol	D-glucose, α-MDG, D-mannose	D-glucose, D-galactose
Inhibitors (pIC_{50})	remogliflozin (pK_i 5.4), sergliflozin (pK_i 5.1), canagliflozin (6.4), dapagliflozin (5.9), empagliflozin (5.1)	remogliflozin (pK_i 7.9), sergliflozin (pK_i 6.8), dapagliflozin (9.0), canagliflozin (8.7), empagliflozin (8.5)	–	–	–
Stoichiometry	2 Na^+ : 1 glucose [129]	1 Na^+ : 1 glucose [127]	–	–	–

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 [142] 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 [127]. Selective blockers of SGLT2, and thus blocking ~50% of renal glucose reabsorption, are in use and in further development for the treatment of diabetes (*e.g.* [113]).

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 [130]. Through recapture of choline generated by the hydrolysis of ACh by acetylcholinesterase, CHT serves to maintain acetylcholine synthesis within the presynaptic terminal [121]. 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 [120]. 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 [140].

Nomenclature	CHT
Systematic nomenclature	SLC5A7
Common abbreviation	CHT
HGNC, UniProt	*SLC5A7*, Q9GZV3
Endogenous substrates	choline
Substrates	triethylcholine
Selective inhibitors (pIC_{50})	hemicholinium-3 (pK_i 8.3 – 9.0)
Radioligands (K_d)	[^{3}H]hemicholinium-3 ($4x10^{-9}$ – $6x10^{-9}$ M)
Stoichiometry	Na^+ : choline (variable stoichimetry); modulated by extracellular Cl^- [128]

Comments: K_i and K_D values for hemicholinium-3 listed in the table are for human CHT expressed in *Xenopus laevis* oocytes [133], or COS-7 cells [109]. 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

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 (T_3) and thyroxine (T_4) [111]. 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 [135]. 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 [122]. 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 [122]. 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 [124]. 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 [132]. 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 [138]. SMCT1 also functions as a tumour suppressor in the colon as well as in various other non-colonic tissues [123]. 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 [139]; 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 [122-123,125]. 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 [137].

Nomenclature	NIS	SMVT	SMCT1	SMCT2
Systematic nomenclature	SLC5A5	SLC5A6	SLC5A8	SLC5A12
Common abbreviation	NIS	SMVT	SMCT1	SMCT2
HGNC, UniProt	*SLC5A5*, Q92911	*SLC5A6*, Q9Y289	*SLC5A8*, Q8N695	*SLC5A12*, Q1EHB4
Substrates	NO_3^-, pertechnetate, perchlorate, thiocyanate, I^-	pantothenic acid [116], I^- [116], biotin [116], lipoic acid [116]	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, β-L-hydroxybutyric acid, pyroglutamic acid, γ-hydroxybutyric acid, pyruvic acid	nicotinic acid, L-lactic acid, pyruvic acid
Inhibitors (pIC_{50})	–	–	fenoprofen, ketoprofen, ibuprofen (4.2)	–
Stoichiometry	$2Na^+$: 1 I^- [119]; $1Na^+$: 1 ClO_4^- [118]	$2Na^+$: 1 biotin (or pantothenic acid) [134]	$2Na^+$: 1 monocarboxylate [114]	–

Comments: I^-, perchlorate, thiocyanate and NO_3^- are competitive substrate inhibitors of NIS [118]. lipoic acid appears to act as a competitive substrate inhibitor of SMVT [141] and the anticonvulsant drugs primidone and carbamazepine competitively block the transport of biotin by brush border vesicles prepared from human intestine [136].

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 [110]. 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 [108].

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-methyl-D-glucopyranoside > D-galactose, D-fucose > D-xylose [126]	*myo*-inositol = D-*chiro*-inositol> D-glucose > D-xylose > L-xylose [115]
Inhibitors (pIC_{50})	phlorizin	phlorizin
Stoichiometry	2 Na^+ :1 *myo*-inositol [126]	2 Na^+ :1 *myo*-inositol [112]

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 [115,126]. 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 [131].

Further reading

Bailey CJ. (2011) Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* **32**: 63–71. [PMID:21211857]

Chao EC, Henry RR. (2010) SGLT2 inhibition–a novel strategy for diabetes treatment. *Nat Rev Drug Discov* **9**: 551–559. [PMID:20508640]

Kinne RK, Castaneda F. (2011) SGLT inhibitors as new therapeutic tools in the treatment of diabetes. *Handb Exp Pharmacol* (**203**): 105–126. [PMID:21484569]

Wright EM. (2013) Glucose transport families SLC5 and SLC50. *Mol Aspects Med* **34**: 183–196. [PMID:23506865]

Wright EM, Loo DD, Hirayama BA. (2011) Biology of human sodium glucose transporters. *Physiol Rev* **91**: 733–794. [PMID:21527736]

SLC6 neurotransmitter transporter family

Overview: Members of the solute carrier family 6 (SLC6) of sodium- and (sometimes chloride-) dependent neurotransmitter transporters [152,156,179] 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 [189]. 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* [206] and in several other transporter families structurally related to LeuT [164].

Monoamine transporter subfamily

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

Nomenclature	Noradrenaline transporter	Dopamine transporter	5HT transporter
Systematic nomenclature	SLC6A2	SLC6A3	SLC6A4
Common abbreviation	NET	DAT	SERT
HGNC, UniProt	*SLC6A2*, P23975	*SLC6A3*, Q01959	*SLC6A4*, P31645
Endogenous substrates	(-)-adrenaline, (-)-noradrenaline, dopamine	(-)-adrenaline, (-)-noradrenaline, dopamine	5-HT
Substrates	MPP^+, methamphetamine, amphetamine	MPP^+, methamphetamine, amphetamine	MDMA, p-chloroamphetamine
Selective inhibitors (pIC_{50})	mazindol (pK_i 8.9), nisoxetine (pK_i 8.4), nomifensine (pK_i 8.1), reboxetine (pK_i 8.0) [205]	mazindol (pK_i 8.0), WIN35428 (pK_i 7.9), GBR12935 (pK_i 7.6)	paroxetine (pK_i 9.6) [198], sertraline (pK_i 9.1), fluoxetine (pK_i 8.5) [198]
Radioligands (K_d)	[^{3}H]mazindol ($5x10^{-10}$ M), [^{3}H]nisoxetine ($4x10^{-9}$ M)	[^{3}H]GBR12935 ($3x10^{-9}$ M) [186], [^{3}H]WIN35428 ($1x10^{-8}$ M) [186]	[^{3}H]paroxetine ($2x10^{-10}$ M), [^{3}H]citalopram ($5x10^{-9}$ M)
Stoichiometry	1 noradrenaline: 1 Na^+:1 Cl^- [171]	1 dopamine: 1–2 Na^+: 1 Cl^- [170]	1 5-HT:1 Na^+:1 Cl^- (in), + 1 K^+ (out) [197]

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 [194].

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 [192]. 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 [181]. 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 [156,172]. CT1, which transports creatine, has a ubiquitous expression pattern, often co-localizing with creatine kinase [156].

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
Endogenous substrates	GABA	GABA, β-alanine	GABA, β-alanine	GABA, betaine	GABA [145], β-alanine, taurine	creatine
Substrates	nipecotic acid, guvacine	nipecotic acid, guvacine	nipecotic acid, guvacine	–	–	–
Selective inhibitors (pIC_{50})	SKF89976A (6.9), CI-966 (6.6), NNC-711 (5.9 – 6.9), tiagabine (5.6 – 7.0), LU32-176B (5.4), (R/S) EF-1500 (4.9 – 5.7), (R)-EF-1520 (5.05 – 5.4), (S)-EF-1520 (3.6 – 3.92)	SNAP-5114 (5.2), SNAP-5114 (4.7)	–	NNC052090 (5.6), (R/S) EF-1500 (4.9), (R)-EF-1520 (3.74 – 4.66), (S)-EF-1520 (3.6 – 4.47), LU32-176B (4.0)	–	–
Radioligands (K_d)	[^{3}H]tiagabine	–	–	–	–	–
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

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 [180]. 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 [157,191] for reviews]. (R)-(1-{2-[tris(4-methoxyphenyl)methoxy]ethyl} pyrrolidin-2-yl)acetic acid is a recently described compound that displays 20-fold selectivity for GAT3 over GAT1 [165]. In addition to the inhibitors listed, EGYT3886 is a moderately potent, though non-selective, inhibitor of all cloned GABA transporters (IC_{50} = 26-46 μM; [160]). 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 [178]. 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 [157,190] for reviews]. GAT3 is inhibited by physiologically relevant concentrations of Zn^{2+} [158]. 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 [161]. Although inhibitors of creatine transport by CT1 (*e.g.* β-guanidinopropionic acid, cyclocreatine, guanidinoethane sulfonic acid) are known (*e.g.* [159]) they insufficiently characterized to be included in the table.

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 [148,163,167,196] for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission [147,166], but also are important, in early neonatal life, for regulating glycine concentrations at inhibitory glycinergic synapses [168]. 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 [168,199]. 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 [207]. 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 [169,188]. Mice in which GlyT2 has been deleted develop a fatal hyperekplexia phenotype during the second postnatal week [169] and mutations in the human gene encoding GlyT2 (SLC6A5) have been identified in patients with hyperekplexia (reviewed by [173]). ATB^{0+} (SLCA14) 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 [156]. ATB^{0+} is expressed in various peripheral tissues [156]. 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	Glycine transporter 1	Glycine transporter 2	$ATB^{0,+}$	Proline transporter
Systematic nomenclature	SLC6A9	SLC6A5	SLC6A14	SLC6A7
Common abbreviation	GlyT1	GlyT2	$ATB^{0,+}$	PROT
HGNC, UniProt	*SLC6A9*, P48067	*SLC6A5*, Q9Y345	*SLC6A14*, Q9UN76	*SLC6A7*, Q99884
Endogenous substrates	glycine, sarcosine	glycine	L-isoleucine > L-leucine, L-methionine > L-phenylalanine > L-tryptophan > L-valine > L-serine [195], β-alanine [144-145]	L-proline
Substrates	–	–	1-methyltryptophan [177], BCH , valganciclovir [200], zwitterionic or cationic NOS inhibitors [174]	–
Selective inhibitors (pIC_{50})	(R)-NFPS (8.5 – 9.1), SSR-103800 (8.7), N-methyl-SSR504734 (8.6), LY2365109 (7.8), GSK931145 (7.6)	ALX 1393, ALX 1405, Org 25543 (7.7)	α-methyl-D,L-tryptophan (3.6) [177]	LP-403812 (7.0) [208]
Radioligands (K_d)	[^{3}H](R)-NPTS ($1x10^{-9}$ M), [^{3}H]GSK931145 ($1.7x10^{-9}$ M), [^{35}S]ACPPB ($2x10^{-9}$ M), [^{3}H]SB-733993 ($2.2x10^{-9}$ M), [^{3}H]N-methyl-SSR504734 ($3.3x10^{-9}$ – $8.1x10^{-9}$ M), [^{3}H]NFPS ($7x10^{-9}$ – $2.1x10^{-8}$ M)	–	–	–
Stoichiometry	2 Na^+: 1 Cl^-: 1 glycine	3 Na^+: 1 Cl^-: 1 glycine	2-3 Na^+: 1 Cl^-: 1 amino acid [195]	Probably 2 Na^+: 1 Cl^-: 1 L-proline
Comment	–	N-Oleoyl-L-carnitine (0.3μM, [155]) and and N-arachidonoylglycine (IC_{50} 5-8 μM, [204]) 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 [210], but has no effect on GlyT2. This difference has been attributed to a single glycine residue in TM6 (serine residue in GlyT2) [202]. Inhibition of GLYT1 by the sarcosine derivatives NFPS, NPTS and Org 24598 is non-competitive [182-183]. IC_{50} values for Org 24598 reported in the literature vary, most likely due to differences in assay conditions [149,182]. The tricyclic antidepressant amoxapine weakly inhibits GlyT2 (IC_{50} 92 μM) with approximately 10-fold selectivity over GlyT1 [184]. The endogenous lipids arachidonic acid and anandamide exert opposing effects upon GlyT1a, inhibiting (IC_{50} ~ 2 μM) and potentiating (EC_{50} ~ 13 μM) transport currents, respectively [185]. N-arachidonyl-glycine, N-arachidonyl-γ-aminobutyric acid and N-arachidonyl-D-alanine have been described as endogenous non-competitive inhibitors of GlyT2a, but not GlyT1b [162,175,204]. Protons [146] and Zn^{2+} [176] act as non-competitive inhibitors of GlyT1b, with IC_{50} values of ~100 nM and ~10 μM respectively, but neither ion affects GlyT2 (reviewed by [201]). Glycine transport by GLYT1 is inhibited by lithium, whereas GLYT2 transport is stimulated (both in the presence of Na^+) [187].

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), SLC6A17, SLC6A18, SLC6A20). Others may function as transporters for neurotransmitters or their precursors (*i.e.* B^0AT2, SLC6A17) [153].

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 [152]	L-proline > L-alanine, L-valine, L-methionine, L-leucine > L-isoleucine, L-threonine, L-asparagine, L-serine, L-phenylalanine > glycine [152]	L-alanine, glycine > L-methionine, L-phenylalanine, L-leucine, L-histidine, L-glutamine [203]	–	L-leucine, L-methionine, L-proline > L-cysteine, L-alanine, L-glutamine, L-serine > L-histidine, glycine [209]	L-proline
Stoichiometry	1 Na^+: 1 amino acid [154]	1 Na^+: 1 amino acid [151]	Na^+- and Cl^- -dependent transport [193]	–	Na^+-dependent, Cl^--independent transport [209]	2 Na^+: 1 Cl^-: 1 imino acid [150]
Comment	Mutations in B^0AT1 are associated with Hartnup disorder	–	–	–	–	–

Further reading

Bröer S, Gether U. (2012) The solute carrier 6 family of transporters. *Br J Pharmacol* **167**: 256–278. [PMID:22519513]

Pramod AB, Foster J, Carvelli L, Henry LK. (2013) SLC6 transporters: structure, function, regulation, disease association and therapeutics. *Mol Aspects Med* **34**: 197–219. [PMID:23506866]

Ramamoorthy S, Shippenberg TS, Jayanthi LD. (2011) Regulation of monoamine transporters: Role of transporter phosphorylation. *Pharmacol Ther* **129**: 220–238. [PMID:20951731]

Rudnick G. (2011) Cytoplasmic permeation pathway of neurotransmitter transporters. *Biochemistry* **50**: 7462–7475. [PMID:21774491]

Zhong H, Sánchez C, Caron MG. (2012) Consideration of allosterism and interacting proteins in the physiological functions of the serotonin transporter. *Biochem Pharmacol* **83**: 435–442. [PMID:21983034]

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.

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) [211]; Reverse mode 1 Ca^{2+} (in): 1 Na^+ (out)	–	–

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 and ORM-10103 [212] act to inhibit NCX function selectively.

Further reading

Annunziato L, Pignataro G, Di Renzo GF. (2004) Pharmacology of brain Na+/Ca2+ exchanger: from molecular biology to therapeutic perspectives. *Pharmacol Rev* **56**: 633–654. [PMID:15602012]

Gabellini N. (2004) Transcriptional regulation by cAMP and Ca2+ links the Na+/Ca2+ exchanger 3 to memory and sensory pathways. *Mol Neurobiol* **30**: 91–116. [PMID:15247490]

Lytton J. (2007) Na+/Ca2+ exchangers: three mammalian gene families control Ca2+ transport. *Biochem J* **406**: 365–382. [PMID:17716241]

Quednau BD, Nicoll DA, Philipson KD. (2004) The sodium/calcium exchanger family-SLC8. *Pflugers Arch* **447**: 543–548. [PMID:12734757]

Watanabe Y, Koide Y, Kimura J. (2006) Topics on the Na+/Ca2+ exchanger: pharmacological characterization of Na+/Ca2+ exchanger inhibitors. *J Pharmacol Sci* **102**: 7–16. [PMID:16990699]

Zhang YH, Hancox JC. (2009) Regulation of cardiac Na+-Ca2+ exchanger activity by protein kinase phosphorylation–still a paradox?. *Cell Calcium* **45**: 1–10. [PMID:18614228]

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 [215–217]. 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 [220] and osteoclasts [214]; gene disruption results in infertile male mice [220].

Nomenclature	Systematic nomenclature	Common abbreviation	HGNC, UniProt
Sodium/hydrogen exchanger 1	SLC9A1	NHE1	*SLC9A1*, P19634
Sodium/hydrogen exchanger 2	SLC9A2	NHE2	*SLC9A2*, Q9UBY0
Sodium/hydrogen exchanger 3	SLC9A3	NHE3	*SLC9A3*, P48764
Sodium/hydrogen exchanger 4	SLC9A4	NHE4	*SLC9A4*, Q6AI14
Sodium/hydrogen exchanger 5	SLC9A5	NHE5	*SLC9A5*, Q14940
Sodium/hydrogen exchanger 6	SLC9A6	NHE6	*SLC9A6*, Q92581
Sodium/hydrogen exchanger 7	SLC9A7	NHE7	*SLC9A7*, Q96T83
Sodium/hydrogen exchanger 8	SLC9A8	NHE8	*SLC9A8*, Q9Y2E8
Sodium/hydrogen exchanger 9	SLC9A9	NHE9	*SLC9A9*, Q8IVB4
solute carrier family 9, subfamily B (NHA1, cation proton antiporter 1), member 1	SLC9B1	NHA1	*SLC9B1*, Q4ZJI4
solute carrier family 9, subfamily B (NHA2, cation proton antiporter 2), member 2	SLC9B2	NHA2	*SLC9B2*, Q86UD5
Sodium/hydrogen exchanger 10	SLC9C1	Sperm-NHE	*SLC9C1*, Q4G0N8
Sodium/hydrogen exchanger 11	SLC9C2	NHE11	*SLC9C2*, Q5TAH2

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 EIPA exhibit a rank order of affinity of inhibition of NHE1 > NHE2 > NHE3 [213,218–219].

Further reading

Bobulescu IA, Moe OW. (2009) Luminal Na(+)/H (+) exchange in the proximal tubule. *Pflugers Arch* **458**: 5–21. [PMID:18853182]

Casey JR, Grinstein S, Orlowski J. (2010) Sensors and regulators of intracellular pH. *Nat Rev Mol Cell Biol* **11**: 50–61. [PMID:19997129]

Donowitz M, Ming Tse C, Fuster D. (2013) SLC9/NHE gene family, a plasma membrane and organellar family of Na^+/H^+ exchangers. *Mol Aspects Med* **34**: 236–251. [PMID:23506868]

Kato A, Romero MF. (2011) Regulation of electroneutral NaCl absorption by the small intestine. *Annu Rev Physiol* **73**: 261–281. [PMID:21054167]

Kemp G, Young H, Fliegel L. (2008) Structure and function of the human Na+/H+ exchanger isoform 1. *Channels (Austin)* **2**: 329–336. [PMID:19001864]

Ohgaki R, van IJzendoorn SC, Matsushita M, Hoekstra D, Kanazawa H. (2011) Organellar Na+/H+ exchangers: novel players in organelle pH regulation and their emerging functions. *Biochemistry* **50**: 443–450. [PMID:21171650]

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 OSTα:OSTβ (SLC51), to maintain the enterohepatic circulation of bile acids [225,234]. SLC10A6 (SOAT) functions as a sodium-dependent transporter of sulphated solutes included sulfphated steroids and bile acids [228,230]. 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 [227,230–231,237]. Members of the SLC10 family are predicted to have seven transmembrane domains with an extracellular N-terminus and cytoplasmic C-terminus [221,232].

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	tauroursodeoxycholic acid, taurocholic acid, taurochenodeoxycholic acid > GCA > cholic acid [235]	GDCA > GUDCA, GCDA > taurocholic acid > cholic acid [224]	pregnenolone sulphate [228], dehydroepiandrosterone sulphate [230], taurolithocholic acid-3-sulphate, estrone-3-sulphate
Endogenous substrates	T_3, dehydroepiandrosterone sulphate [224,227,235], estrone-3-sulphate, iodothyronine sulphates	–	–
Radioligands (K_d)	–	[^{3}H]taurocholic acid [224]	–
Stoichiometry	2 Na^+: 1 bile acid [221,228]	>1 Na^+: 1 bile acid [224,238]	–
Comment	chenodeoxycholyl-N$^\varepsilon$-nitrobenzoxadiazol-lysine is a fluorescent bile acid analogue used as a probe [229].	–	–
Inhibitors (pIC_{50})	cyclosporin A [226,233], irbesartan [226], propranolol [224]	SC-435 (8.82) [222], 264W94 (7.32) [236,239]	–

Nomenclature	Sodium/bile acid and sulphated solute cotransporter 3	Sodium/bile acid and sulphated solute cotransporter 4	Sodium/bile acid and sulphated solute cotransporter 5	Sodium/bile acid and sulphated solute cotransporter 7
Systematic nomenclature	SLC10A3	SLC10A4	SLC10A5	SLC10A7
Common abbreviation	P3	P4	P5	P7
HGNC, UniProt	*SLC10A3*, P09131	*SLC10A4*, Q96EP9	*SLC10A5*, Q5PT55	*SLC10A7*, Q0GE19

Comments: Heterologously expressed SLC10A4 [229] or SLC10A7 [231] failed to exhibit significant transport of taurocholic acid, pregnenolone sulphate, DHEAS or choline. SLC10A4 has recently been suggested to associate with neuronal vesicles [223].

Further reading

Borges K. (2013) Slc10A4 - what do we know about the function of this "secret ligand carrier" protein?. *Exp Neurol* **248C**: 258–261 [Epub ahead of print]. [PMID:23810836]

Claro da Silva T, Polli JE, Swaan PW. (2013) The solute carrier family 10 (SLC10): beyond bile acid transport. *Mol Aspects Med* **34**: 252–269. [PMID:23506869]

Dawson PA, Lan T, Rao A. (2009) Bile acid transporters. *J Lipid Res* **50**: 2340–2357. [PMID:19498215]

Döring B, Lütteke T, Geyer J, Petzinger E. (2012) The SLC10 carrier family: transport functions and molecular structure. *Curr Top Membr* **70**: 105–168. [PMID:23177985]

Zwicker BL, Agellon LB. (2013) Transport and biological activities of bile acids. *Int J Biochem Cell Biol* **45**: 1389–1398. [PMID:23603607]

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. SLC11A1/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	Fe^{2+}, Mn^{2+}	Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Mn^{2+}
Stoichiometry	1 H^+ : 1 Fe^{2+} (out) or 1 Fe^{2+} (in) : 1 H^+ (out)	1 H^+ : 1 Fe^{2+} (out) [240]

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

Li X, Yang Y, Zhou F, Zhang Y, Lu H, Jin Q, Gao L. (2011) SLC11A1 (NRAMP1) polymorphisms and tuberculosis susceptibility: updated systematic review and meta-analysis. *PLoS ONE* **6**: e15831. [PMID:21283567]

Mackenzie B, Hediger MA. (2004) SLC11 family of H+-coupled metal-ion transporters NRAMP1 and DMT1. *Pflugers Arch* **447**: 571–579. [PMID:14530973]

Montalbetti N, Simonin A, Kovacs G, Hediger MA. (2013) Mammalian iron transporters: families SLC11 and SLC40. *Mol Aspects Med* **34**: 270–287. [PMID:23506870]

Nevo Y, Nelson N. (2006) The NRAMP family of metal-ion transporters. *Biochim Biophys Acta* **1763**: 609–620. [PMID:16908340]

Zheng W, Monnot AD. (2012) Regulation of brain iron and copper homeostasis by brain barrier systems: implication in neurodegenerative diseases. *Pharmacol Ther* **133**: 177–188. [PMID:22115751]

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
Systematic nomenclature	SLC12A1	SLC12A2	SLC12A3
Common abbreviation	NKCC2	NKCC1	NCC
HGNC, UniProt	*SLC12A1*, Q13621	*SLC12A2*, P55011	*SLC12A3*, P55017
Inhibitors (pIC_{50})	bumetanide [242], furosemide [242], piretanide [242]	bumetanide [242], furosemide [242], piretanide [242]	chlorothiazide, hydrochlorothiazide, metolazone
Stoichiometry	1 Na^+ : 1 K^+ : 2 Cl^- (in)	1 Na^+ : 1 K^+ : 2 Cl^- (in)	1 Na^+ : 1 Cl^- (in)

Nomenclature	K-Cl cotransporter 1	K-Cl cotransporter 2	K-Cl cotransporter 3	K-Cl cotransporter 4
Systematic nomenclature	SLC12A4	SLC12A5	SLC12A6	SLC12A7
Common abbreviation	KCC1	KCC2	KCC3	KCC4
HGNC, UniProt	*SLC12A4*, Q9UP95	*SLC12A5*, Q9H2X9	*SLC12A6*, Q9UHW9	*SLC12A7*, Q9Y666
Inhibitors (pIC_{50})	DIOA	DIOA, VU0240551 [241]	DIOA	DIOA
Stoichiometry	1 K^+ : 1 Cl^- (out)	1 K^+ : 1 Cl^- (out)	1 K^+ : 1 Cl^- (out)	1 K^+ : 1 Cl^- (out)

Nomenclature	Cation-chloride cotransporter 9	Cation-chloride cotransporter 6
Systematic nomenclature	SLC12A8	SLC12A9
Common abbreviation	CCC9	CCC6
HGNC, UniProt	*SLC12A8*, A0AV02	*SLC12A9*, Q9BXP2
Substrates	spermine, L-glutamic acid, spermidine, L-aspartic acid	–
Stoichiometry	Unknown	–
Comment	–	CCC6 is regarded as an orphan transporter

Comments: DIOA is able to differentiate KCC isoforms from NKCC and NCC transporters, but also inhibits CFTR [243].

Further reading

Arroyo JP, Kahle KT, Gamba G. (2013) The SLC12 family of electroneutral cation-coupled chloride cotransporters. *Mol Aspects Med* **34**: 288–298. [PMID:23506871]

Gagnon KB, Delpire E. (2013) Physiology of SLC12 transporters: lessons from inherited human genetic mutations and genetically engineered mouse knockouts. *Am J Physiol, Cell Physiol* **304**: C693–C714. [PMID:23325410]

Gamba G, Friedman PA. (2009) Thick ascending limb: the Na(+):K (+):2Cl (-) co-transporter, NKCC2, and the calcium-sensing receptor, CaSR. *Pflugers Arch* **458**: 61–76. [PMID:18982348]

Hebert SC, Mount DB, Gamba G. (2004) Molecular physiology of cation-coupled Cl^- cotransport: the SLC12 family. *Pflugers Arch* **447**: 580–593. [PMID:12739168]

Kahle KT, Rinehart J, Lifton RP. (2010) Phosphoregulation of the Na-K-2Cl and K-Cl cotransporters by the WNK kinases. *Biochim Biophys Acta* **1802**: 1150–1158. [PMID:20637866]

Lang F, Vallon V, Knipper M, Wangemann P. (2007) Functional significance of channels and transporters expressed in the inner ear and kidney. *Am J Physiol, Cell Physiol* **293**: C1187–C1208. [PMID:17670895]

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	SeO_4^{2-}, $S_2O_3^{2-}$, SO_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

Further reading

Lee A, Dawson PA, Markovich D. (2005) NaSi-1 and Sat-1: structure, function and transcriptional regulation of two genes encoding renal proximal tubular sulfate transporters. *Int J Biochem Cell Biol* **37**: 1350–1356. [PMID:15833267]

Markovich D. (2011) Physiological roles of renal anion transporters NaS1 and Sat1. *Am J Physiol Renal Physiol* **300**: F1267–F1270. [PMID:21490138]

Markovich D, Aronson PS. (2007) Specificity and regulation of renal sulfate transporters. *Annu Rev Physiol* **69**: 361–375. [PMID:17002596]

Markovich D, Murer H. (2004) The SLC13 gene family of sodium sulphate/carboxylate cotransporters. *Pflugers Arch* **447**: 594–602. [PMID:12915942]

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 [245]. 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
Endogenous substrates	ammonium carbonate [246], urea [246], formamide [246]	urea [244]
Substrates	acrylamide [246], acetamide [246], methylurea [246]	–
Stoichiometry	Equilibrative	Equilibrative

Further reading

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–R503. [PMID:23364530]

Shayakul C, Clémençon B, Hediger MA. (2013) The urea transporter family (SLC14): physiological, pathological and structural aspects. *Mol Aspects Med* **34**: 313–322. [PMID:23506873]

Shayakul C, Hediger MA. (2004) The SLC14 gene family of urea transporters. *Pflugers Arch* **447**: 603–609. [PMID:12856182]

Smith CP. (2009) Mammalian urea transporters. *Exp Physiol* **94**: 180–185. [PMID:19028811]

Stewart G. (2011) The emerging physiological roles of the SLC14A family of urea transporters. *Br J Pharmacol* **164**: 1780–1792. [PMID:21449978]

SLC15 family of peptide transporters

Overview: The SLC15 family of peptide transporters may be divided on the basis of structural and functional differences into two subfamilies: SLC15A1 (PepT1) and SLC15A2 (PepT2) transport di- and tripeptides, but not amino acids, whereas SLC15A3 (PHT2) and SLC15A4 (PHT1) transport L-histidine and some di- and tripeptides [251]. The transporters are 12 TM proteins with intracellular termini and an extended extracellular loop at TM 9/10. The crystal structure of PepTSo (a prokaryote homologue of PepT1 and PepT2 from *Shewanella oneidensis*) confirms many of the predicted structural features of mammalian PepT1 and PepT2 [261].

PHT1 has been suggested to be intracellular [262], while PHT2 protein is located on lysosomes in transfected cells [250,257,264]. PHT1 is hypothesised to mediate efflux of bacterial-derived peptides into the cytosol perhaps in the colon where SLC15A4 mRNA expression is increased in inflammatory bowel disease [259]. Transport via PHT1 may be important in immune responses as both Toll-like receptor- and NOD1-mediated responses are reduced in PHT1 knockout mice or mouse strains expressing mutations in PHT1 [249,265].

Nomenclature	Peptide transporter 1	Peptide transporter 2	Peptide transporter 3	Peptide transporter 4
Systematic nomenclature	SLC15A1	SLC15A2	SLC15A3	SLC15A4
Common abbreviation	PepT1	PepT2	PHT2	PHT1
HGNC, UniProt	*SLC15A1*, P46059	*SLC15A2*, Q16348	*SLC15A3*, Q8IY34	*SLC15A4*, Q8N697
Endogenous substrates	5-aminolevulinic acid [253], dipeptides [253], tripeptides [253]	5-aminolevulinic acid, dipeptides, tripeptides	L-histidine, carnosine, dipeptides, tripeptides	L-histidine, carnosine, dipeptides, tripeptides
Substrates	fMet-Leu-Phe [260], cyclacillin [254], valacyclovir [255], cefadroxil [254], muramyl dipeptide [268]	cyclacillin [254], cefadroxil [254]	–	valacyclovir [247]
Inhibitors (pIC_{50})	4-AMBA [252], Lys[Z(NO_2)]-Pro [258]	Lys[Z(NO_2)]-Lys[Z(NO_2)] [248,267], Lys[Z(NO_2)]-Pro	–	–
Radioligands (K_d)	[^{11}C]GlySar, [^{14}C]GlySar, [^{3}H]GlySar	[^{11}C]GlySar, [^{14}C]GlySar, [^{3}H]GlySar	[^{14}C]histidine, [^{3}H]histidine	[^{14}C]histidine, [^{3}H]histidine
Stoichiometry	1 H^+ : 1 zwitterionic peptide (in)	2 H^+ : 1 zwitterionic peptide (in)	Unknown	Unknown

Comments: The PepT1 and PepT2 transporters are particularly promiscuous in the transport of dipeptides and tripeptides from the endogenous amino acids, as well as some D-amino acid containing peptides. PepT1 has also been exploited to allow delivery of therapeutic pro-drugs, such as those for zidovudine [256], sulpiride [269] and cytarabine [266].

D-Ala-Lys-AMCA has been used as a fluorescent probe to identify transport via both PepT1 and PepT2 [263].

Further reading

Anderson CM, Thwaites DT. (2010) Hijacking solute carriers for proton-coupled drug transport. *Physiol (Bethesda)* **25**: 364–377. [PMID:21186281]

Biegel A, Knütter I, Hartrodt B, Gebauer S, Theis S, Luckner P, Kottra G, Rastetter M, Zebisch K, Thondorf I *et al*. (2006) The renal type H+/peptide symporter PEPT2: structure-affinity relationships. *Amino Acids* **31**: 137–156. [PMID:16868651]

Brandsch M. (2009) Transport of drugs by proton-coupled peptide transporters: pearls and pitfalls. *Expert Opin Drug Metab Toxicol* **5**: 887–905. [PMID:19519280]

Ingersoll SA, Ayyadurai S, Charania MA, Laroui H, Yan Y, Merlin D. (2012) The role and pathophysiological relevance of membrane transporter PepT1 in intestinal inflammation and inflammatory bowel disease. *Am J Physiol Gastrointest Liver Physiol* **302**: G484–G492. [PMID:22194420]

Smith DE, Clémençon B, Hediger MA. (2013) Proton-coupled oligopeptide transporter family SLC15: physiological, pharmacological and pathological implications. *Mol Aspects Med* **34**: 323–336. [PMID:23506874]

Thwaites DT, Anderson CM. (2007) H+-coupled nutrient, micronutrient and drug transporters in the mammalian small intestine. *Exp Physiol* **92**: 603–619. [PMID:17468205]

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 4	Monocarboxylate transporter 2	Monocarboxylate transporter 3
Systematic nomenclature	SLC16A1	SLC16A3	SLC16A7	SLC16A8
Common abbreviation	MCT1	MCT4	MCT2	MCT3
HGNC, UniProt	*SLC16A1*, P53985	*SLC16A3*, O15427	*SLC16A7*, O60669	*SLC16A8*, O95907
Endogenous substrates	β-D-hydroxybutyric acid, L-lactic acid, pyruvic acid	L-lactic acid, pyruvic acid	L-lactic acid, pyruvic acid	L-lactic acid
Substrates	γ-hydroxybutyric acid [272]	–	–	–
Stoichiometry	1 H^+: 1 monocarboxylate$^-$ (out)	1 H^+: 1 monocarboxylate$^-$ (out)	1 H^+: 1 monocarboxylate$^-$ (out)	1 H^+: 1 monocarboxylate$^-$ (out)

Nomenclature	Monocarboxylate transporter 8	Monocarboxylate transporter 10
Systematic nomenclature	SLC16A2	SLC16A10
Common abbreviation	MCT8	TAT1
HGNC, UniProt	*SLC16A2*, P36021	*SLC16A10*, Q8TF71
Endogenous substrates	T_3 [270], T_4 [270]	L-tryptophan, L-phenylalanine, L-DOPA, L-tyrosine
Stoichiometry	Unknown	Unknown

Nomenclature	Monocarboxylate transporter 5	Monocarboxylate transporter 6	Monocarboxylate transporter 7	Monocarboxylate transporter 9	Monocarboxylate transporter 11	Monocarboxylate transporter 12	Monocarboxylate transporter 13	Monocarboxylate transporter 14
Systematic nomenclature	SLC16A4	SLC16A5	SLC16A6	SLC16A9	SLC16A11	SLC16A12	SLC16A13	SLC16A14
Common abbreviation	MCT5	MCT6	MCT7	MCT9	MCT11	MCT12	MCT13	MCT14
HGNC, UniProt	*SLC16A4*, O15374	*SLC16A5*, O15375	*SLC16A6*, O15403	*SLC16A9*, Q7RTY1	*SLC16A11*, Q8NCK7	*SLC16A12*, Q6ZSM3	*SLC16A13*, Q7RTY0	*SLC16A14*, Q7RTX9
Stoichiometry	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Comment	–	MCT6 has been reported to transport bumetanide, but not short chain fatty acids [271]	–	–	–	–	–	–

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

Anderson CM, Thwaites DT. (2010) Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* **25**: 364–377. [PMID:21186281]

Braun D, Wirth EK, Schweizer U. (2010) Thyroid hormone transporters in the brain. *Rev Neurosci* **21**: 173–186. [PMID:20879691]

Friesema EC, Visser WE, Visser TJ. (2010) Genetics and phenomics of thyroid hormone transport by MCT8. *Mol Cell Endocrinol* **322**: 107–113. [PMID:20083155]

Halestrap AP, Meredith D. (2004) The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. *Pflugers Arch* **447**: 619–628. [PMID:12739169]

Heuer H, Visser TJ. (2009) Minireview: Pathophysiological importance of thyroid hormone transporters. *Endocrinology* **150**: 1078–1083. [PMID:19179441]

Jansen J, Friesema EC, Milici C, Visser TJ. (2005) Thyroid hormone transporters in health and disease. *Thyroid* **15**: 757–768. [PMID:16131319]

Meredith D, Christian HC. (2008) The SLC16 monocaboxylate transporter family. *Xenobiotica* **38**: 1072–1106. [PMID:18668440]

Morris ME, Felmlee MA. (2008) Overview of the proton-coupled MCT (SLC16A) family of transporters: characterization, function and role in the transport of the drug of abuse gamma-hydroxybutyric acid. *AAPS J* **10**: 311–321. [PMID:18523892]

van der Deure WM, Peeters RP, Visser TJ. (2010) Molecular aspects of thyroid hormone transporters, including MCT8, MCT10, and OATPs, and the effects of genetic variation in these transporters. *J Mol Endocrinol* **44**: 1–11. [PMID:19541799]

Visser TJ. (2007) Thyroid hormone transporters. *Horm Res* **68 Suppl 5**: 28–30. [PMID:18174701]

Visser WE, Friesema EC, Jansen J, Visser TJ. (2008) Thyroid hormone transport in and out of cells. *Trends Endocrinol Metab* **19**: 50–56. [PMID:18291666]

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

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	Cl^- [275], probenecid [274], PO_3^{4-} [275], uric acid [275], penicillin G [274], organic acids [275]	–	–	–
Stoichiometry	Unknown	Unknown	Unknown	Unknown

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 [277], 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) [277], L-lactic acid, L-aspartic acid [277], 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 [279].

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 [273].

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 [276].

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 [278].

Nomenclature	Vesicular nucleotide transporter
Systematic nomenclature	SLC17A9
Common abbreviation	VNUT
HGNC, UniProt	*SLC17A9*, Q9BYT1
Endogenous substrates	ATP [278], GTP [278], GDP [278]
Stoichiometry	Unknown

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

Further reading

Biber J, Hernando N, Forster I. (2013) Phosphate transporters and their function. *Annu Rev Physiol* **75**: 535–550. [PMID:23398154]

El Mestikawy S, Wallén-Mackenzie A, Fortin GM, Descarries L, Trudeau LE. (2011) From glutamate co-release to vesicular synergy: vesicular glutamate transporters. *Nat Rev Neurosci* **12**: 204–216. [PMID:21415847]

Marks J, Debnam ES, Unwin RJ. (2010) Phosphate homeostasis and the renal-gastrointestinal axis. *Am J Physiol Renal Physiol* **299**: F285–F296. [PMID:20534868]

Miyamoto K, Haito-Sugino S, Kuwahara S, Ohi A, Nomura K, Ito M, Kuwahata M, Kido S, Tatsumi S, Kaneko I *et al.* (2011) Sodium-dependent phosphate cotransporters: lessons from gene knockout and mutation studies. *J Pharm Sci* **100**: 3719–3730. [PMID:21567407]

Omote H, Miyaji T, Juge N, Moriyama Y. (2011) Vesicular neurotransmitter transporter: bioenergetics and regulation of glutamate transport. *Biochemistry* **50**: 5558–5565. [PMID:21612282]

Reimer RJ. (2013) SLC17: a functionally diverse family of organic anion transporters. *Mol Aspects Med* **34**: 350–359. [PMID:23506876]

Shobeiri N, Adams MA, Holden RM. (2013) Phosphate: an old bone molecule but new cardiovascular risk factor. *Br J Clin Pharmacol* [Epub ahead of print]. [PMID:23506202]

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 multisubunit vacuolar ATPase that acidifies secretory vesicles (reviewed by [283]). The vesicular acetylcholine transporter (VAChT; [287]) localizes to cholinergic neurons, but non-neuronal expression has also been claimed [290]. Vesicular monoamine transporter 1 (VMAT1, [285]) is mainly expressed in peripheral neuroendocrine cells, but most likely not in the CNS, whereas VMAT2 [286] distributes between both central and peripheral sympathetic monoaminergic neurones [284].

Nomenclature	Vesicular monoamine transporter 1	Vesicular monoamine transporter 2	Vesicular acetylcholine transporter	solute carrier family 18, subfamily B, member 1
Systematic nomenclature	SLC18A1	SLC18A2	SLC18A3	SLC18B1
Common abbreviation	VMAT1	VMAT2	VAChT	–
HGNC, UniProt	*SLC18A1*, P54219	*SLC18A2*, Q05940	*SLC18A3*, Q16572	*SLC18B1*, Q6NT16
Endogenous substrates	5-HT (Ki $1.4x10^{-6}$ M) [286], (-)-adrenaline (Ki $5.5x10^{-6}$ M) [286], (-)-noradrenaline (Ki $1.37x10^{-5}$ M) [286], dopamine (Ki $3.8x10^{-6}$ M) [286], histamine (Ki $4.696x10^{-3}$ M) [286]	5-HT (Ki $9x10^{-7}$ M) [286], (-)-adrenaline (Ki $1.9x10^{-6}$ M) [286], (-)-noradrenaline (Ki $3.4x10^{-6}$ M) [286], dopamine (Ki $1.4x10^{-6}$ M) [286], histamine (Ki $1.43x10^{-4}$ M) [286]	acetylcholine (Ki $7.94x10^{-4}$ M) [280,288], choline (Ki $5x10^{-4}$ M) [280,288]	–
Substrates	β-phenylethylamine (Ki $3.4x10^{-5}$ M) [286], dextroamphetamine (Ki $4.7x10^{-5}$ M) [286], MPP^+ (Ki $6.9x10^{-5}$ M) [286], MDMA (Ki $1.9x10^{-5}$ M) [286], fenfluramine (Ki $3.1x10^{-6}$ M) [286]	β-phenylethylamine (Ki $3.7x10^{-6}$ M) [286], dextroamphetamine (Ki $2.1x10^{-6}$ M) [286], MPP^+ (Ki $8.9x10^{-6}$ M) [286], MDMA (Ki $6.9x10^{-6}$ M) [286], fenfluramine (Ki $5.1x10^{-6}$ M) [286]	TPP^+ [281], ethidium [281], N-methyl-pyridinium-2-aldoxime [281], N-(4′-pentanonyl)-4-(4″-dimethylamino-styryl)pyridinium [281]	–
Inhibitors (pIC_{50})	reserpine (pK_i 7.45) [286], ketanserin (pK_i 5.8) [286], tetrabenazine (pK_i 4.7) [286]	reserpine (pK_i 7.9) [286], tetrabenazine (pK_i 7.0) [286], ketanserin (pK_i 6.3) [286]	aminobenzovesamicol (pK_i 10.9) [282], vesamicol (pK_i 8.7) [282]	–
Radioligands (K_d)	–	[^{11}C]DTBZ, [^{125}I]8-azido-3-iodoketanserine, [^{3}H]TBZOH ($6.6x10^{-9}$ M) [291], [^{125}I]iodovinyl-TBZ ($8.2x10^{-9}$ M) [289]	[^{123}I]iodobenzovesamicol, [^{3}H]vesamicol ($4.1x10^{-9}$ M) [291]	–
Stoichiometry	1 amine (in): $2H^+$ (out)	1 amine (in): $2H^+$ (out)	1 amine (in): $2H^+$ (out)	–

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 [286]. In addition to the monoamines listed in the table, the trace amines tyramine and β-phenylethylamine are probable substrates for VMAT2 [284]. Probes listed in the table are those currently employed; additional agents have been synthesized (*e.g.* [292]).

Further reading

Chaudhry FA, Edwards RH, Fonnum F. (2008) Vesicular neurotransmitter transporters as targets for endogenous and exogenous toxic substances. *Annu Rev Pharmacol Toxicol* **48**: 277–301. [PMID:17883368]

Eiden LE, Weihe E. (2011) VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. *Ann N Y Acad Sci* **1216**: 86–98. [PMID:21272013]

Giboureau N, Som IM, Boucher-Arnold A, Guilloteau D, Kassiou M. (2010) PET radioligands for the vesicular acetylcholine transporter (VAChT). *Curr Top Med Chem* **10**: 1569–1583. [PMID:20583990]

Khare P, White AR, Mulakaluri A, Parsons SM. (2010) Equilibrium binding and transport by vesicular acetylcholine transporter. *Methods Mol Biol* **637**: 181–219. [PMID:20419436]

Lawal HO, Krantz DE. (2013) SLC18: Vesicular neurotransmitter transporters for monoamines and acetylcholine. *Mol Aspects Med* **34**: 360–372. [PMID:23506877]

Prado VF, Roy A, Kolisnyk B, Gros R, Prado MA. (2013) Regulation of cholinergic activity by the vesicular acetylcholine transporter. *Biochem J* **450**: 265–274. [PMID:23410039]

Ramamoorthy S, Shippenberg TS, Jayanthi LD. (2011) Regulation of monoamine transporters: Role of transporter phosphorylation. *Pharmacol Ther* **129**: 220–238. [PMID:20951731]

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

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
Endogenous substrates	thiamine monophosphate [298], tetrahydrofolic acid [296], N^5-methylfolate [296], Organic phosphates; in particular, adenine nucleotides, Other tetrahydrofolate-cofactors	thiamine	thiamine
Substrates	folic acid [296], methotrexate, folinic acid, N^5-formyltetrahydrofolate	–	–
Radioligands (K_d)	[^{3}H]folic acid [293], [^{3}H]methotrexate [293]	[^{3}H]thiamine [295]	[^{3}H]thiamine [297]
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

Comments: Loss-of-function mutations in ThTr1 underlie thiamine-responsive megaloblastic anemia syndrome [294].

Further reading

Ganapathy V, Smith SB, Prasad PD. (2004) SLC19: the folate/thiamine transporter family. *Pflugers Arch* **447**: 641–646. [PMID:14770311]

Goldman ID, Chattopadhyay S, Zhao R, Moran R. (2010) The antifolates: evolution, new agents in the clinic, and how targeting delivery via specific membrane transporters is driving the development of a next generation of folate analogs. *Curr Opin Investig Drugs* **11**: 1409–1423. [PMID:21154123]

Matherly LH, Hou Z. (2008) Structure and function of the reduced folate carrier a paradigm of a major facilitator superfamily mammalian nutrient transporter. *Vitam Horm* **79**: 145–184. [PMID:18804694]

Yuasa H, Inoue K, Hayashi Y. (2009) Molecular and functional characteristics of proton-coupled folate transporter. *J Pharm Sci* **98**: 1608–1616. [PMID:18823045]

Zhao R, Diop-Bove N, Visentin M, Goldman ID. (2011) Mechanisms of membrane transport of folates into cells and across epithelia. *Annu Rev Nutr* **31**: 177–201. [PMID:21568705]

Zhao R, Goldman ID. (2013) Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors. *Mol Aspects Med* **34**: 373–385. [PMID:23506878]

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 PO_3^{4-} and vitamin D regulation of parathyroid hormone secretion from the parathyroid gland. PiT2 appears to be involved in intestinal absorption of dietary PO_3^{4-}.

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-} [299], PO_3^{4-} [299]	PO_3^{4-} [299]
Stoichiometry	>1 Na^+ : 1 HPO_4^{2-} (in)	>1 Na^+ : 1 HPO_4^{2-} (in)

Further reading

Biber J, Hernando N, Forster I. (2013) Phosphate transporters and their function. *Annu Rev Physiol* **75**: 535–550. [PMID:23398154]

Forster IC, Hernando N, Biber J, Murer H. (2013) Phosphate transporters of the SLC20 and SLC34 families. *Mol Aspects Med* **34**: 386–395. [PMID:23506879]

Marks J, Debnam ES, Unwin RJ. (2010) Phosphate homeostasis and the renal-gastrointestinal axis. *Am J Physiol Renal Physiol* **299**: F285-F296. [PMID:20534868]

Miyamoto K, Haito-Sugino S, Kuwahara S, Ohi A, Nomura K, Ito M, Kuwahata M, Kido S, Tatsumi S, Kaneko I *et al.* (2011) Sodium-dependent phosphate cotransporters: lessons from gene knockout and mutation studies. *J Pharm Sci* **100**: 3719–3730. [PMID:21567407]

Shobeiri N, Adams MA, Holden RM. (2013) Phosphate: an old bone molecule but new cardiovascular risk factor. *Br J Clin Pharmacol* [Epub ahead of print]. [PMID:23506202]

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)

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
Endogenous substrates	5-HT, PGE_2, $PGF_{2\alpha}$, choline	dopamine [303], histamine [303], PGE_2 [304]	5-HT [307], (-)-noradrenaline [307], dopamine [307]
Substrates	tetraethylammonium, desipramine, MPP^+, metformin, acyclovir	(+)-tubocurarine [302], tetraethylammonium [302], pancuronium [302], MPP^+ [302]	quinidine, tetraethylammonium, MPP^+
Stoichiometry	Unknown	Unknown	Unknown

Comments: corticosterone and quinine are able to inhibit all three organic cation 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
Endogenous substrates	L-carnitine	acetyl-L-carnitine, L-carnitine	L-carnitine
Substrates	pyrilamine, tetraethylammonium, verapamil, MPP^+	pyrilamine, tetraethylammonium, verapamil, MPP^+	–
Stoichiometry	Unknown	Unknown	Unknown

Organic anion transporters (OATs)

Overview: Organic anion transporters (OATs) are non-selective transporters prominent in the kidney and intestine.

Nomenclature	Organic anion transporter 1	Organic anion transporter 2	Organic anion transporter 3	Organic anion transporter 7	Organic anion transporter 5	Organic anion transporter 4
Systematic nomenclature	SLC22A6	SLC22A7	SLC22A8	SLC22A9	SLC22A10	SLC22A11
Common abbreviation	OAT1	OAT2	OAT3	OAT4	OAT5	–
HGNC, UniProt	*SLC22A6*, Q4U2R8	*SLC22A7*, Q9Y694	*SLC22A8*, Q8TCC7	*SLC22A9*, Q8IVM8	*SLC22A10*, Q63ZE4	*SLC22A11*, Q9NSA0
Substrates	aminohippuric acid, non-steroidal anti-inflammatory drugs	PGE_2, aminohippuric acid, non-steroidal anti-inflammatory drugs	cimetidine [305], ochratoxin A [305], estrone-3-sulphate [305], aminohippuric acid [305]	–	ochratoxin A [306]	dehydroepiandrosterone sulphate [300], ochratoxin A [300], estrone-3-sulphate [300]
Stoichiometry	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown

Urate transporter

Nomenclature	Urate anion exchanger 1
Systematic nomenclature	SLC22A12
Common abbreviation	URAT1
HGNC, UniProt	*SLC22A12*, Q96S37
Endogenous substrates	orotic acid [301], uric acid [301]
Stoichiometry	Unknown

Orphan or poorly characterized SLC22 family members

Nomenclature	Systematic nomenclature	Common abbreviation	HGNC, UniProt
Organic cation transporter-like 3	SLC22A13	ORCTL3	*SLC22A13*, Q9Y226
Organic cation transporter-like 4	SLC22A14	ORCTL4	*SLC22A14*, Q9Y267
Fly-like putative transporter 1	SLC22A15	FLIPT1	*SLC22A15*, Q8IZD6
Brain-type organic cation transporter	SLC22A17	BOIT	*SLC22A17*, Q8WUG5
Organic cation transporter-like 2	SLC22A18	ORCTL2	*SLC22A18*, Q96BI1
OAT6	SLC22A20	–	*SLC22A20*, A6NK97
–	SLC22A23	–	*SLC22A23*, A1A5C7
–	SLC22A24	–	*SLC22A24*, Q8N4F4
UST6	SLC22A25	–	*SLC22A25*, Q6T423
solute carrier family 22, member 31	SLC22A31	–	*SLC22A31*, A6NKX4

Further reading

Burckhardt G. (2012) Drug transport by Organic Anion Transporters (OATs). *Pharmacol Ther* **136**: 106–130. [PMID:22841915]

Koepsell H. (2013) The SLC22 family with transporters of organic cations, anions and zwitterions. *Mol Aspects Med* **34**: 413–435. [PMID:23506881]

König J, Müller F, Fromm MF. (2013) Transporters and drug-drug interactions: important determinants of drug disposition and effects. *Pharmacol Rev* **65**: 944–966. [PMID:23686349]

Motohashi H, Inui K. (2013) Organic cation transporter OCTs (SLC22) and MATEs (SLC47) in the human kidney. *AAPS J* **15**: 581–588. [PMID:23435786]

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.

Nomenclature	Sodium-dependent vitamin C transporter 1	Sodium-dependent vitamin C transporter 2	Sodium-dependent vitamin C transporter 3	Sodium-dependent nucleobase transporter
Systematic nomenclature	SLC23A1	SLC23A2	SLC23A3	SLC23A4
Common abbreviation	SVCT1	SVCT2	SVCT3	SNBT1
HGNC, UniProt	*SLC23A1*, Q9UHI7	*SLC23A2*, Q9UGH3	*SLC23A3*, Q6PIS1	*SLC23A4P*, –
Endogenous substrates	L-ascorbic acid > D-ascorbic acid > dehydroascorbic acid [308]	L-ascorbic acid > D-ascorbic acid > dehydroascorbic acid [308]	–	uracil > thymine > guanine, hypoxanthine > xanthine, uridine [309]
Substrates	–	–	–	–
Inhibitors (pIC_{50})	phloretin [308]	–	–	5-fluorouracil [309]
Radioligands (K_d)	[^{14}C]ascorbic acid	[^{14}C]ascorbic acid	–	–
Stoichiometry	2 Na^+: 1 ascorbic acid (in) [308]	2 Na^+: 1 ascorbic acid (in) [308]	–	1 Na^+ : 1 uracil (in) [309]
Comment	–	–	SLC23A3 does not transport ascorbic acid and remains an orphan transporter.	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

Bürzle M, Suzuki Y, Ackermann D, Miyazaki H, Maeda N, Clémençon B, Burrier R, Hediger MA. (2013) The sodium-dependent ascorbic acid transporter family SLC23. *Mol Aspects Med* **34**: 436–454. [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**: 1793–1801. [PMID:21418192]

Rivas CI, Zúñiga FA, Salas-Burgos A, Mardones L, Ormazabal V, Vera JC. (2008) Vitamin C transporters. *J Physiol Biochem* **64**: 357–375. [PMID:19391462]

Savini I, Rossi A, Pierro C, Avigliano L, Catani MV. (2008) SVCT1 and SVCT2: key proteins for vitamin C uptake. *Amino Acids* **34**: 347–355. [PMID:17541511]

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 2	Sodium/potassium/calcium exchanger 3	Sodium/potassium/calcium exchanger 4	Sodium/potassium/calcium exchanger 5	Sodium/potassium/calcium exchanger 6
Systematic nomenclature	SLC24A1	SLC24A2	SLC24A3	SLC24A4	SLC24A5	SLC24A6
Common abbreviation	NKCX1	NKCX2	NKCX3	NKCX4	NKCX5	NKCX6
HGNC, UniProt	*SLC24A1*, O60721	*SLC24A2*, Q9UI40	*SLC24A3*, Q9HC58	*SLC24A4*, Q8NFF2	*SLC24A5*, Q71RS6	*SLC8B1*, Q6J4K2
Stoichiometry	$4Na^+$:($1Ca^{2+}$ + $1K^+$)	–	–	–	–	–

Comments: NKCX6 exhibits sufficient structural diversity for its function as a NKCX to be questioned [310].

To date, there are no agents selective for this family of transporters.

Further reading

Altimimi HF, Schnetkamp PP. (2007) Na+/Ca2+-K+ exchangers (NCKX): functional properties and physiological roles. *Channels (Austin)* **1**: 62–69. [PMID:18690016]

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**: 455–464. [PMID:23506883]

SLC25 family of mitochondrial transporters

Overview: Mitochondrial transporters are nuclear-encoded proteins, which convey solutes across the inner mitochondrial membrane. Topological modelling suggests homodimeric transporters, each with six TM segments and termini in the cytosol.

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	SLC25A34	SLC25A35
Common abbreviation	CIC	DIC	OGC	ODC	–	–
HGNC, UniProt	*SLC25A1*, P53007	*SLC25A10*, Q9UBX3	*SLC25A11*, Q02978	*SLC25A21*, Q9BQT8	*SLC25A34*, Q6PIV7	*SLC25A35*, Q3KQZ1
Substrates	citric acid, malic acid, PEP	malic acid, succinic acid, PO_3^{4-}, $S_2O_3^{2-}$, SO_4^{2-}	malic acid, α-ketoglutaric acid	α-ketoglutaric acid, α-oxoadipic acid	–	–
Inhibitors (pIC_{50})	1,2,3-benzenetricarboxylic 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)	–	–

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	Mitochondrial glutamate carrier 1	Mitochondrial glutamate carrier 2	AGC1	AGC2
Systematic nomenclature	SLC25A22	SLC25A18	SLC25A12	SLC25A13
Common abbreviation	GC1	GC2	AGC1	AGC2
HGNC, UniProt	*SLC25A22*, Q9H936	*SLC25A18*, Q9H1K4	*SLC25A12*, O75746	*SLC25A13*, Q9UJS0
Substrates	L-glutamic acid	L-glutamic acid	L-glutamic acid, L-aspartic acid, 2-amino-3-sulfinopropanoic acid	L-glutamic acid, L-aspartic acid, 2-amino-3-sulfinopropanoic acid
Stoichiometry	Glutamate : H^+ (bidirectional)	Glutamate : H^+ (bidirectional)	Aspartate : glutamate H^+ (bidirectional)	Aspartate : glutamate H^+ (bidirectional)

Nomenclature	Mitochondrial ornithine transporter 1	Mitochondrial ornithine transporter 2	Carnitine/acylcarnitine carrier
Systematic nomenclature	SLC25A15	SLC25A2	SLC25A20
Common abbreviation	ORC1	ORC2	CAC
HGNC, UniProt	*SLC25A15*, Q9Y619	*SLC25A2*, Q9BXI2	*SLC25A20*, O43772
Substrates	L-arginine [311], L-citrulline [311], L-lysine [311], L-ornithine [311]	L-arginine [311], L-citrulline [311], L-lysine [311], L-ornithine [311], L-histidine [311], D-histidine [311], D-arginine [311], D-lysine [311], D-ornithine [311], D-citrulline [311]	–
Stoichiometry	1 Ornithine (in) :1 citrulline : 1 H^+ (out)	1 Ornithine (in) :1 citrulline : 1 H^+ (out)	–
Comment	–	–	Exchanges cytosolic acylcarnitine for mitochondrial carnitine

Nomenclature	solute carrier family 25, member 47	solute carrier family 25, member 48	ORNT3	–	CGI-69	MCFP	–	–
Systematic nomenclature	SLC25A47	SLC25A48	SLC25A29	SLC25A38	SLC25A39	SLC25A40	SLC25A44	SLC25A45
Common abbreviation	–	–	ORNT3	–	–	–	–	–
HGNC, UniProt	*SLC25A47*, Q6Q0C1	*SLC25A48*, Q6ZT89	*SLC25A29*, Q8N8R3	*SLC25A38*, Q96DW6	*SLC25A39*, Q9BZJ4	*SLC25A40*, Q8TBP6	*SLC25A44*, Q96H78	*SLC25A45*, Q8N413

Comments: Both ornithine transporters are inhibited by the polyamine spermine [312]. Loss-of-function mutations in these genes are associated with hyperornithinemia-hyperammonemia-homocitrullinuria.

Mitochondrial phosphate transporters

Overview: Mitochondrial phosphate transporters allow the import of inorganic PO_3^{4-} 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

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	–
Systematic nomenclature	SLC25A4	SLC25A5	SLC25A6	SLC25A31	SLC25A42
Common abbreviation	ANT1	ANT2	ANT3	ANT4	–
HGNC, UniProt	*SLC25A4*, P12235	*SLC25A5*, P05141	*SLC25A6*, P12236	*SLC25A31*, Q9H0C2	*SLC25A42*, Q86VD7
Inhibitors (pIC_{50})	BKA, CATR	–	–	–	–
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)	–
Substrates	–	–	–	–	ADP

Nomenclature	Graves disease carrier	Peroxisomal membrane protein	Deoxynucleotide carrier 1	S-Adenosylmethionine carrier
Systematic nomenclature	SLC25A16	SLC25A17	SLC25A19	SLC25A26
Common abbreviation	GDC	PMP34	DNC	SAMC1
HGNC, UniProt	*SLC25A16*, P16260	*SLC25A17*, O43808	*SLC25A19*, Q9HC21	*SLC25A26*, Q70HW3
Substrates	CoA and congeners	ADP, ATP, AMP	Deoxynucleotide Diphosphates (dNDPs), Deoxynucleotide Triphosphates (dNTPs), Dideoxynucleotide Triphosphates (ddNTPs), Nucleotide Diphosphates (NDPs)	S-adenosyl methionine
Stoichiometry	CoA (in)	ATP (in)	dNDP (in) : ATP (out)	–

Nomenclature	Mitochondrial phosphate carrier 1	Mitochondrial phosphate carrier 2	Mitochondrial phosphate carrier 3	MFT	PNC1	–	SCaMC-3L	–
Systematic nomenclature	SLC25A24	SLC25A23	SLC25A25	SLC25A32	SLC25A33	SLC25A36	SLC25A41	SLC25A43
Common abbreviation	APC1	APC2	APC3	MFTC	–	PNC2	–	–
HGNC, UniProt	*SLC25A24*, Q6NUK1	*SLC25A23*, Q9BV35	*SLC25A25*, Q6KCM7	*SLC25A32*, Q9H2D1	*SLC25A33*, Q9BSK2	*SLC25A36*, Q96CQ1	*SLC25A41*, Q8N5S1	*SLC25A43*, Q8WUT9

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
Systematic nomenclature	SLC25A7	SLC25A8	SLC25A9
Common abbreviation	UCP1	UCP2	UCP3
HGNC, UniProt	*UCP1*, P25874	*UCP2*, P55851	*UCP3*, P55916
Stoichiometry	H^+ (in)	H^+ (in)	H^+ (in)

Nomenclature	Uncoupling protein 4	Uncoupling protein 5	KMCP1
Systematic nomenclature	SLC25A27	SLC25A14	SLC25A30
Common abbreviation	UCP4	UCP5	–
HGNC, UniProt	*SLC25A27*, O95847	*SLC25A14*, O95258	*SLC25A30*, Q5SVS4
Stoichiometry	H^+ (in)	H^+ (in)	–

Miscellaneous SLC25 mitochondrial transporters

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

Nomenclature	mitochondrial carrier 1	mitochondrial carrier 2	Mitoferrin1	Mitoferrin2
Systematic nomenclature	SLC25A49	SLC25A50	SLC25A37	SLC25A28
HGNC, UniProt	*MTCH1*, Q9NZJ7	*MTCH2*, Q9Y6C9	*SLC25A37*, Q9NYZ2	*SLC25A28*, Q96A46

Nomenclature	solute carrier family 25, member 51	solute carrier family 25, member 52	solute carrier family 25, member 53	–
Systematic nomenclature	SLC25A51	SLC25A52	SLC25A53	SLC25A46
HGNC, UniProt	*SLC25A51*, Q9H1U9	*SLC25A52*, Q3SY17	*SLC25A53*, Q5H9E4	*SLC25A46*, Q96AG3

Further reading

Cioffi F, Senese R, de Lange P, Goglia F, Lanni A, Lombardi A. (2009) Uncoupling proteins: a complex journey to function discovery. *Biofactors* **35**: 417–428. [PMID:19626697]

Clémençon B, Babot M, Trézéguet V. (2013) The mitochondrial ADP/ATP carrier (SLC25 family): pathological implications of its dysfunction. *Mol Aspects Med* **34**: 485–493. [PMID:23506884]

Gnoni GV, Priore P, Geelen MJ, Siculella L. (2009) The mitochondrial citrate carrier: metabolic role and regulation of its activity and expression. *IUBMB Life* **61**: 987–994. [PMID:19787704]

Gutiérrez-Aguilar M, Baines CP. (2013) Physiological and pathological roles of mitochondrial SLC25 carriers. *Biochem J* **454**: 371–386. [PMID:23988125]

Palmieri F. (2004) The mitochondrial transporter family (SLC25): physiological and pathological implications. *Pflugers Arch* **447**: 689–709. [PMID:14598172]

Palmieri F. (2013) The mitochondrial transporter family SLC25: identification, properties and physiopathology. *Mol Aspects Med* **34**: 465–484. [PMID:23266187]

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

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

Chloride/bicarbonate exchangers

Nomenclature	DRA	Pendrin	PAT-1
Systematic nomenclature	SLC26A3	SLC26A4	SLC26A6
HGNC, UniProt	*SLC26A3*, P40879	*SLC26A4*, O43511	*SLC26A6*, Q9BXS9
Substrates	Cl^-	Cl^-, HCO_3^-, formate, I^-, OH^-	Cl^-, HCO_3^-, SO_4^{2-}, oxalate, formate, I^-, OH^-
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

Systematic 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 [315]	Voltage- and time-independent current, linear I-V relationship [314]
Comment	–	SLC26A9 has been suggested to operate in two additional modes as a Cl^--HCO_3^- exchanger and as a Na^+-anion cotransporter [313]

Other SLC26 anion exchangers

Nomenclature	Prestin	Tat1	–	KBAT
Systematic nomenclature	SLC26A5	SLC26A8	SLC26A10	SLC26A11
Common abbreviation	–	–	–	KBAT
HGNC, UniProt	*SLC26A5*, P58743	*SLC26A8*, Q96RN1	*SLC26A10*, Q8NG04	*SLC26A11*, Q86WA9
Substrates	Cl^-, HCO_3^-	Cl^-, SO_4^{2-}, oxalate	–	HSO_4^-
Stoichiometry	Unknown	Unknown	Unknown	Unknown
Comment	Prestin has been suggested to function as a molecular motor, rather than a transporter	–	SLC26A10 is a possible pseudogene	–

Further reading

Alper SL, Sharma AK. (2013) The SLC26 gene family of anion transporters and channels. *Mol Aspects Med* **34**: 494–515. [PMID:23506885]

Dorwart MR, Shcheynikov N, Yang D, Muallem S. (2008) The solute carrier 26 family of proteins in epithelial ion transport. *Physiology (Bethesda)* **23**: 104–114. [PMID:18400693]

Kato A, Romero MF. (2011) Regulation of electroneutral NaCl absorption by the small intestine. *Annu Rev Physiol* **73**: 261–281. [PMID:21054167]

Mount DB, Romero MF. (2004) The SLC26 gene family of multifunctional anion exchangers. *Pflugers Arch* **447**: 710–721. [PMID:12759755]

Nofziger C, Dossena S, Suzuki S, Izuhara K, Paulmichl M. (2011) Pendrin function in airway epithelia. *Cell Physiol Biochem* **28**: 571–578. [PMID:22116372]

Ohana E, Yang D, Shcheynikov N, Muallem S. (2009) Diverse transport modes by the solute carrier 26 family of anion transporters. *J Physiol (Lond)* **587** (Pt 10): 2179–2185. [PMID:19015189]

Soleimani M. (2013) SLC26 Cl(-)/HCO3(-) exchangers in the kidney: roles in health and disease. *Kidney Int* [Epub ahead of print]. [PMID:23636174]

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 [319,325], 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) [317,322–323]. 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 [321,325].

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 [325], palmitic acid > oleic acid > γ-linolenic acid > octanoic acid [318]	–	–	palmitic acid > oleic acid > butyric acid, γ-linolenic acid > arachidonic acid [326], palmitic acid, oleic acid > γ-linolenic acid > octanoic acid [318]	–	palmitic acid > oleic acid > γ-linolenic acid > octanoic acid [318]
Comment	–	–	–	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 [320,324] and FATP4 [316,327], as well as bile acid inhibitors of FATP5 [327], 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

Anderson CM, Stahl A. (2013) SLC27 fatty acid transport proteins. *Mol Aspects Med* **34**: 516–528. [PMID:23506886]

Schwenk RW, Holloway GP, Luiken JJ, Bonen A, Glatz JF. (2010) Fatty acid transport across the cell membrane: regulation by fatty acid transporters. *Prostaglandins Leukot Essent Fatty Acids* **82**: 149–154. [PMID:20206486]

SLC28 and SLC29 families of nucleoside transporters

Overview: Nucleoside transporters are divided into two families, the sodium-dependent, solute carrier family 28 (SLC28) and the equilibrative, solute carrier family 29 (SLC29), where the endogenous substrates are nucleosides.

SLC28 family

Overview: SLC28 family members have 13 TM segments with cytoplasmic N-termini and extracellular C-termini.

Nomenclature	CNT1	CNT2	CNT3
Systematic nomenclature	SLC28A1	SLC28A2	SLC28A3
Common abbreviation	CNT1	CNT2	CNT3
HGNC, UniProt	*SLC28A1*, O00337	*SLC28A2*, O43868	*SLC28A3*, Q9HAS3
Endogenous substrates	adenosine, uridine, thymidine, cytidine	adenosine, inosine, guanosine, thymidine	adenosine, inosine, uridine, guanosine, thymidine, cytidine
Substrates	gemcitabine, zidovudine, zalcitabine	formycin B, cladribine, fludarabine, vidarabine, didanosine	5-fluorouridine, zebularine, formycin B, gemcitabine, cladribine, floxuridine, zidovudine, zalcitabine, didanosine
Stoichiometry	1 Na^+ : 1 nucleoside (in)	1 Na^+ : 1 nucleoside (in)	2 Na^+ : 1 nucleoside (in)

Comments: A further two Na^+-dependent (stoichiometry 1 Na^+ : 1 nucleoside (in)) nucleoside transporters have been defined on the basis of substrate and inhibitor selectivity: CNT4 (N4/*cit*, which transports uridine, thymidine and guanosine) and CNT5 (N5/*csg*, which transports guanosine and adenosine, and may be inhibited by NBTI).

SLC29 family

Overview: SLC29 family members appear to be composed of 11 TM segments with cytoplasmic N-termini and extracellular C-termini. ENT1 and ENT2 are cell-surface transporters, while ENT3 is intracellular, possibly lysosomal [328]. ENT1-3 are described as broad-spectrum nucleoside transporters.

Nomenclature	Equilibrative nucleoside transporter 1	Equilibrative nucleoside transporter 2	Equilibrative nucleoside transporter 3	Plasma membrane monoamine transporter
Systematic nomenclature	SLC29A1	SLC29A2	SLC29A3	SLC29A4
Common abbreviation	ENT1	ENT2	ENT3	PMAT
HGNC, UniProt	*SLC29A1*, Q99808	*SLC29A2*, Q14542	*SLC29A3*, Q9BZD2	*SLC29A4*, Q7RTT9
Endogenous substrates	adenosine [335], inosine [335], hypoxanthine [335], uridine [335], guanosine [335], thymine [335], thymidine [335], cytidine [335], adenine [335]	adenosine, inosine, hypoxanthine, uridine, guanosine, thymidine	adenosine [328], inosine [328], uridine [328], guanosine [328], thymidine [328], adenine [328]	5-HT [329], dopamine [329], histamine [329], tyramine [329]

Nomenclature	Equilibrative nucleoside transporter 1	Equilibrative nucleoside transporter 2	Equilibrative nucleoside transporter 3	Plasma membrane monoamine transporter
Substrates	2-chloroadenosine, formycin B, tubercidin, gemcitabine, cladribine, floxuridine, pentostatin, vidarabine, cytarabine, zalcitabine, didanosine	2-chloroadenosine, formycin B, tubercidin, gemcitabine, cladribine, vidarabine, zidovudine, cytarabine	cordycepin [328], zebularine [328], tubercidin [328], cladribine [328], floxuridine [328], fludarabine [328], zidovudine [328], zalcitabine [328], didanosine [328]	tetraethylammonium [329], MPP^+ [329]
Inhibitors (pIC_{50})	NBTI (pK_i 9.7), draflazine (pK_i 9.5), KF24345 (pK_i 9.4) [330], NBTGR (pK_i 9.3), dilazep (pK_i 9.0), dipyridamole (pK_i 8.5)	–	–	cimetidine [329], quinidine [329], quinine [329], rhodamine123 [329], verapamil [329]
Radioligands (K_d)	[^{3}H]NBTI ($5x10^{-10}$ M)	–	–	–
Stoichiometry	Equilibrative	Equilibrative	Equilibrative	Equilibrative
Comment	ENT1 has 100-1000-fold lower affinity for nucleobases as compared with nucleosides [335]., The affinities of draflazine, dilazep, KF24345 and dipyridamole at ENT1 transporters are species dependent, exhibiting lower affinity at rat transporters than at human transporters [330,333]., The loss of ENT1 activity in ENT1-null mice has been associated with a hypermineralization disorder similar to human diffuse idiopathic skeletal hyperostosis [334]	–	Defects in SLC29A3 have been implicated in Histiocytosis-lymphadenopathy plus syndrome (OMIM:602782) and lysosomal storage diseases [331–332]	–

Further reading

Baldwin SA, McConkey GA, Cass CE, Young JD. (2007) Nucleoside transport as a potential target for chemotherapy in malaria. *Curr Pharm Des* **13**: 569–580. [PMID:17346175]

Cano-Soldado P, Pastor-Anglada M. (2012) Transporters that translocate nucleosides and structural similar drugs: structural requirements for substrate recognition. *Med Res Rev* **32**: 428–457. [PMID:21287570]

King AE, Ackley MA, Cass CE, Young JD, Baldwin SA. (2006) Nucleoside transporters: from scavengers to novel therapeutic targets. *Trends Pharmacol Sci* **27**: 416–425. [PMID:16820221]

Pastor-Anglada M, Cano-Soldado P, Errasti-Murugarren E, Casado FJ. (2008) SLC28 genes and concentrative nucleoside transporter (CNT) proteins. *Xenobiotica* **38**: 972–994. [PMID:18668436]

Young JD, Yao SY, Baldwin JM, Cass CE, Baldwin SA. (2013) The human concentrative and equilibrative nucleoside transporter families, SLC28 and SLC29. *Mol Aspects Med* **34**: 529–547. [PMID:23506887]

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 [337], 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 [336]. The mechanism for zinc transport is unknown.

Nomenclature	Systematic nomenclature	Common abbreviation	HGNC, UniProt
Zinc transporter 1	SLC30A1	ZnT1	*SLC30A1*, Q9Y6M5
Zinc transporter 2	SLC30A2	ZnT2	*SLC30A2*, Q9BRI3
Zinc transporter 3	SLC30A3	ZnT3	*SLC30A3*, Q99726
Zinc transporter 4	SLC30A4	ZnT4	*SLC30A4*, O14863
Zinc transporter 5	SLC30A5	ZnT5	*SLC30A5*, Q8TAD4
Zinc transporter 6	SLC30A6	ZnT6	*SLC30A6*, Q6NXT4
Zinc transporter 7	SLC30A7	ZnT7	*SLC30A7*, Q8NEW0
Zinc transporter 8	SLC30A8	ZnT8	*SLC30A8*, Q8IWU4
Zinc transporter 9	SLC30A9	ZnT9	*SLC30A9*, Q6PML9
Zinc transporter 10	SLC30A10	ZnT10	*SLC30A10*, Q6XR72

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

Bouron A, Oberwinkler J. (2013) Contribution of calcium-conducting channels to the transport of zinc ions. *Pflugers Arch* [Epub ahead of print]. [PMID:23719866]

Huang L, Tepaamorndech S. (2013) The SLC30 family of zinc transporters - a review of current understanding of their biological and pathophysiological roles. *Mol Aspects Med* **34**: 548–560. [PMID:23506888]

Kawasaki E. (2012) ZnT8 and type 1 diabetes. *Endocr J* **59**: 531–537. [PMID:22447136]

Palmiter RD, Huang L. (2004) Efflux and compartmentalization of zinc by members of the SLC30 family of solute carriers. *Pflugers Arch* **447**: 744–751. [PMID:12748859]

Rungby J. (2010) Zinc, zinc transporters and diabetes. *Diabetologia* **53**: 1549–1551. [PMID:20490449]

Wang X, Zhou B. (2010) Dietary zinc absorption: A play of Zips and ZnTs in the gut. *IUBMB Life* **62**: 176–182. [PMID:20120011]

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 [341]. 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 [340].

Nomenclature	Copper transporter 1	Copper transporter 2
Systematic nomenclature	SLC31A1	SLC31A2
Common abbreviation	CTR1	CTR2
HGNC, UniProt	*SLC31A1*, O15431	*SLC31A2*, O15432
Endogenous substrates	copper [340]	copper
Substrates	cisplatin [339]	cisplatin [338]
Stoichiometry	Unknown	Unknown

Comments: Copper accumulation through CTR1 is sensitive to silver ions, but not divalent cations [340].

Further reading

Howell SB, Safaei R, Larson CA, Sailor MJ. (2010) Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. *Mol Pharmacol* **77**: 887–894. [PMID:20159940]

Kim H, Wu X, Lee J. (2013) SLC31 (CTR) family of copper transporters in health and disease. *Mol Aspects Med* **34**: 561–570. [PMID:23506889]

Nose Y, Rees EM, Thiele DJ. (2006) Structure of the Ctr1 copper trans'PORE'ter reveals novel architecture. *Trends Biochem Sci* **31**: 604–607. [PMID:16982196]

Petris MJ. (2004) The SLC31 (Ctr) copper transporter family. *Pflugers Arch* **447**: 752–755. [PMID:12827356]

Zheng W, Monnot AD. (2012) Regulation of brain iron and copper homeostasis by brain barrier systems: implication in neurodegenerative diseases. *Pharmacol Ther* **133**: 177–188. [PMID:22115751]

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 [343–344], and is a member of the structurally-defined amino acid-polyamine-organocation/APC clan composed of SLC32, SLC36 and SLC38 transporter families (see [349]). VIAAT was originally suggested to be composed of 10 TM segments with cytoplasmic N- and C-termini [347]. 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 [346]. 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 (Δψ) components of the proton electrochemical gradient ($\Delta\mu_{H}+$) established by a vacuolar H^+-ATPase [347]. However, one study, [345], 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 [342,351]. VIAAT knock out mice die between embryonic day 18.5 and birth [350]. 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 [348,350].

Nomenclature	Vesicular inhibitory amino acid transporter
Systematic nomenclature	SLC32A1
Common abbreviation	VIAAT
HGNC, UniProt	*SLC32A1*, Q9H598
Endogenous substrates	glycine, β-alanine, γ-hydroxybutyric acid, GABA (Km $5x10^{-3}$ M) [347]
Inhibitors (pIC_{50})	vigabatrin (2.1) [347]
Stoichiometry	1 amino acid (in): 1 H^+ (out) [344] or 1 amino acid: $2Cl^-$ (in) [345]

Further reading

Erickson JD, De Gois S, Varoqui H, Schafer MK, Weihe E. (2006) Activity-dependent regulation of vesicular glutamate and GABA transporters: a means to scale quantal size. *Neurochem Int* **48**: 643–649. [PMID:16546297]

Gasnier B. (2000) The loading of neurotransmitters into synaptic vesicles. *Biochimie* **82**: 327–337. [PMID:10865121]

Gasnier B. (2004) The SLC32 transporter, a key protein for the synaptic release of inhibitory amino acids. *Pflugers Arch* **447**: 756–759. [PMID:12750892]

Schiöth HB, Roshanbin S, Hägglund MG, Fredriksson R. (2013) Evolutionary origin of amino acid transporter families SLC32, SLC36 and SLC38 and physiological, pathological and therapeutic aspects. *Mol Aspects Med* **34**: 571–585. [PMID:23506890]

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 [353], 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
Radioligands (K_d)	[^{14}C]acetylCoA
Stoichiometry	Unknown

Comments: In heterologous expression studies, acetyl CoA transport through AT1 was inhibited by coenzyme A, but not acetic acid, ATP or UDP-galactose [352]. A loss-of-function mutation in ACATN1/SLC33A1 has been associated with spastic paraplegia (SPG42, [354]), although this observation could not be replicated in a subsequent study [355].

Further reading

Hirabayashi Y, Kanamori A, Nomura KH, Nomura K. (2004) The acetyl-CoA transporter family SLC33. *Pflugers Arch* **447**: 760–762. [PMID:12739170]

Hirabayashi Y, Nomura KH, Nomura K. (2013) The acetyl-CoA transporter family SLC33. *Mol Aspects Med* **34**: 586–589. [PMID:23506891]

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 [356].

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) [357]	3 Na^+ : 1 HPO_4^{2-} (in) [356]	2 Na^+ : 1 HPO_4^{2-} (in) [356]

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

Further reading

Biber J, Hernando N, Forster I. (2013) Phosphate transporters and their function. *Annu Rev Physiol* **75**: 535–550. [PMID:23398154]

Forster IC, Hernando N, Biber J, Murer H. (2013) Phosphate transporters of the SLC20 and SLC34 families. *Mol Aspects Med* **34**: 386–395. [PMID:23506879]

Marks J, Debnam ES, Unwin RJ. (2010) Phosphate homeostasis and the renal-gastrointestinal axis. *Am J Physiol Renal Physiol* **299**: F285–F296. [PMID:20534868]

Miyamoto K, Haito-Sugino S, Kuwahara S, Ohi A, Nomura K, Ito M, Kuwahata M, Kido S, Tatsumi S, Kaneko I *et al*. (2011) Sodium-dependent phosphate cotransporters: lessons from gene knockout and mutation studies. *J Pharm Sci* **100**: 3719–3730. [PMID:21567407]

Murer H, Forster I, Biber J. (2004) The sodium phosphate cotransporter family SLC34. *Pflugers Arch* **447**: 763–767. [PMID:12750889]

Shobeiri N, Adams MA, Holden RM. (2013) Phosphate: an old bone molecule but new cardiovascular risk factor. *Br J Clin Pharmacol* [Epub ahead of print]. [PMID:23506202]

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	MGC2541	FLJ11130
Systematic nomenclature	SLC35A1	SLC35A2	SLC35A3	SLC35A4	SLC35A5
HGNC, UniProt	*SLC35A1*, P78382	*SLC35A2*, P78381	*SLC35A3*, Q9Y2D2	*SLC35A4*, Q96G79	*SLC35A5*, Q9BS91
Substrates	CMP-sialic acid [359]	UDP N-acetyl-glucosamine [361,366], UDP-galactose [361,366]	UDP N-acetyl-glucosamine [362]	–	–

Nomenclature	UGTREL1	PAPS transporter 1	PAPS transporter 2	YEA
Systematic nomenclature	SLC35B1	SLC35B2	SLC35B3	SLC35B4
HGNC, UniProt	*SLC35B1*, P78383	*SLC35B2*, Q8TB61	*SLC35B3*, Q9H1N7	*SLC35B4*, Q969S0
Substrates	–	A3P5PS [364]	A3P5PS [363]	UDP N-acetyl-glucosamine [358], UDP-xylose [358]

Nomenclature	GDP-Fucose transporter	OVCOV1	UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter	HFRC1	FRCL1
Systematic nomenclature	SLC35C1	SLC35C2	SLC35D1	SLC35D2	SLC35D3
HGNC, UniProt	*SLC35C1*, Q96A29	*SLC35C2*, Q9NQQ7	*SLC35D1*, Q9NTN3	*SLC35D2*, Q76EJ3	*SLC35D3*, Q5M8T2
Substrates	GDP-fucose [365]	–	UDP-glucuronic acid [367], UDP-N-acetylgalactosamine [367]	UDP-N-acetylgalactosamine [360]	–

Nomenclature	–	–	solute carrier family 35, member E2B	–	–
Systematic nomenclature	SLC35E1	SLC35E2	SLC35E2B	SLC35E3	SLC35E4
HGNC, UniProt	*SLC35E1*, Q96K37	*SLC35E2*, P0CK97	*SLC35E2B*, P0CK96	*SLC35E3*, Q7Z769	*SLC35E4*, Q6ICL7
Comment	Orphan transporter	Orphan transporter	–	Orphan transporter	Orphan transporter

Nomenclature	–	–	–	–	–	solute carrier family 35, member F6
Systematic nomenclature	SLC35F1	SLC35F2	SLC35F3	SLC35F4	SLC35F5	SLC35F6
HGNC, UniProt	*SLC35F1*, Q5T1Q4	*SLC35F2*, Q8IXU6	*SLC35F3*, Q8IY50	*SLC35F4*, A4IF30	*SLC35F5*, Q8WV83	*SLC35F6*, Q8N357
Comment	Orphan transporter	Orphan transporter	Orphan transporter	Orphan transporter	Orphan transporter	–

Nomenclature	solute carrier family 35, member G1	solute carrier family 35, member G3	solute carrier family 35, member G4	solute carrier family 35, member G5	solute carrier family 35, member G6
Systematic nomenclature	SLC35G1	SLC35G3	SLC35G4	SLC35G5	SLC35G6
HGNC, UniProt	*SLC35G1*, Q2M3R5	*SLC35G3*, Q8N808	*SLC35G4*, P0C7Q5	*SLC35G5*, Q96KT7	*SLC35G6*, P0C7Q6

Further reading

Ishida N, Kawakita M. (2004) Molecular physiology and pathology of the nucleotide sugar transporter family (SLC35). *Pflugers Arch* **447**: 768–775. [PMID:12759756]

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

Overview: The SLC36 family of proton-coupled amino acid transporters (or PAT) is highly expressed in the intestine and kidney, having roles in the disposition of amino acids [383]. PAT1 is found on the gut epithelia luminal surface accumulating dietary amino acids, and additionally in lysosomal membranes where it likely functions as an efflux mechanism for amino acids produced during intralysosomal proteolysis [369,382]. PAT2 is found at the apical membrane of the kidney proximal tubule [372]. PAT1 and PAT2 are predicted to have 11 TM domains with intracellular N-termini [370,382].

Nomenclature	Proton-coupled Amino acid Transporter 1	Proton-coupled Amino acid Transporter 2	Proton-coupled Amino acid Transporter 3	Proton-coupled Amino acid Transporter 4
Systematic nomenclature	SLC36A1	SLC36A2	SLC36A3	SLC36A4
Common abbreviation	PAT1	PAT2	PAT3	PAT4
HGNC, UniProt	*SLC36A1*, Q7Z2H8	*SLC36A2*, Q495M3	*SLC36A3*, Q495N2	*SLC36A4*, Q6YBV0
Endogenous substrates	L-alanine, glycine, GABA, β-alanine, taurine, L-proline, D-serine, D-cysteine, D-proline, D-alanine, trans-4-hydroxy-proline, sarcosine	L-alanine, glycine, β-alanine, L-proline, trans-4-hydroxy-proline, sarcosine	–	L-tryptophan [381], L-proline [381]
Substrates	THIP [378], betaine, L-azetidine-2-carboxylate [377], MeAIB [373], β-guanidinopropionic acid, THPO [379], 5-aminolevulinic acid, vigabatrin [368]	L-azetidine-2-carboxylate [377], MeAIB [374]	–	–
Inhibitors (pIC_{50})	5-hydroxy-L-tryptophan (pK_i 3.0) [380], indole-3-propionic acid (pK_i 2.3) [380], L-tryptophan (pK_i 2.3) [380], 5-HT (pK_i 2.2) [380]	5-hydroxy-L-tryptophan (2.8) [375], α-methyl-D,L-tryptophan (2.5) [375]	–	–
Stoichiometry	1 H^+ : 1 amino acid (in)	1 H^+ : 1 amino acid (in)	Unknown	Unknown
Comment	[^{3}H] or [^{14}C] labelled substrates as listed above are used as probes	[^{3}H] or [^{14}C] labelled substrates as listed above are used as probes	–	–

Comments: Both PAT1 and PAT2 can also function as an electroneutral transport system for H^+ and fatty acids including acetic acid, propanoic acid and butyric acid [376].

Loss-of-function mutations in PAT2 lead to iminoglycinuria and hyperglycinuria in man [371].

Further reading

Boll M, Daniel H, Gasnier B. (2004) The SLC36 family: proton-coupled transporters for the absorption of selected amino acids from extracellular and intracellular proteolysis. *Pflugers Arch* **447**: 776–779. [PMID:12748860]

Schiöth HB, Roshanbin S, Hägglund MG, Fredriksson R. (2013) Evolutionary origin of amino acid transporter families SLC32, SLC36 and SLC38 and physiological, pathological and therapeutic aspects. *Mol Aspects Med* **34**: 571–585. [PMID:23506890]

Thwaites DT, Anderson CM. (2007) Deciphering the mechanisms of intestinal imino (and amino) acid transport: the redemption of SLC36A1. *Biochim Biophys Acta* **1768**: 179–197. [PMID:17123464]

Thwaites DT, Anderson CM. (2011) The SLC36 family of proton-coupled amino acid transporters and their potential role in drug transport. *Br J Pharmacol* **164**: 1802–1816. [PMID:21501141]

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	SPX2	SPX3	Glucose-6-phosphate transporter
Systematic nomenclature	SLC37A1	SLC37A2	SLC37A3	SLC37A4
Common abbreviation	SPX1	–	–	SPX4
HGNC, UniProt	*SLC37A1*, P57057	*SLC37A2*, Q8TED4	*SLC37A3*, Q8NCC5	*SLC37A4*, O43826
Endogenous substrates	glucose 6-phosphate, glycerol 3-phosphate	glucose 6-phosphate	–	glucose 6-phosphate
Stoichiometry	Glucose 6-phosphate (in): phosphate (out) [386]	Glucose 6-phosphate (in): phosphate (out) [386]	Unknown	Glucose 6-phosphate (in): phosphate (out) [385]
Comment	–	–	–	Multiple polymorphisms have been described for the SLC37A4 gene, some of which associate with a glycogen storage disease [384]

Further reading

Bartoloni L, Antonarakis SE. (2004) The human sugar-phosphate/phosphate exchanger family SLC37. *Pflugers Arch* **447**: 780–783. [PMID:12811562]

Chou JY, Sik Jun H, Mansfield BC. (2013) The SLC37 family of phosphate-linked sugar phosphate antiporters. *Mol Aspects Med* **34**: 601–611. [PMID:23506893]

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 [394].

System A-like transporters

Nomenclature	SNAT1	SNAT2	SNAT4
Systematic nomenclature	SLC38A1	SLC38A2	SLC38A4
Common abbreviation	SNAT1	SNAT2	SNAT4
HGNC, UniProt	*SLC38A1*, Q9H2H9	*SLC38A2*, Q96QD8	*SLC38A4*, Q969I6
Endogenous substrates	L-alanine > L-serine, L-glutamine, L-asparagine, L-histidine, L-cysteine, L-methionine > glycine, L-threonine, L-proline, L-tyrosine, L-valine [387]	L-alanine, L-methionine > L-asparagine, L-glutamine, L-serine, L-proline, glycine > L-threonine, L-leucine, L-phenylalanine [391]	L-histidine > L-arginine, L-alanine, L-asparagine, L-lysine > glycine, L-glutamine, L-serine, L-proline, L-leucine, L-phenylalanine [390]
Substrates	MeAIB	MeAIB	MeAIB
Radioligands (K_d)	[^{14}C]alanine, [^{3}H]alanine	[^{14}C]alanine, [^{3}H]alanine	[^{14}C]alanine, [^{14}C]glycine, [^{3}H]alanine, [^{3}H]glycine
Stoichiometry	1 Na^+ : 1 amino acid (in) [387]	1 Na^+ : 1 amino acid (in) [391]	1 Na^+ : 1 neutral amino acid (in) [390]
Comment	–	–	Transport of cationic amino acids by SNAT4 was sodium-independent [390]

System N-like transporters

Nomenclature	SNAT3	SNAT5
Systematic nomenclature	SLC38A3	SLC38A5
Common abbreviation	SNAT3	SNAT5
HGNC, UniProt	*SLC38A3*, Q99624	*SLC38A5*, Q8WUX1
Endogenous substrates	L-histidine , L-glutamine > L-asparagine, L-alanine > L-glutamic acid [389]	L-asparagine, L-serine, L-histidine, L-glutamine > glycine, L-alanine [393]
Substrates	MeAIB	MeAIB
Radioligands (K_d)	[^{14}C]glutamine, [^{3}H]glutamine	[^{14}C]histidine, [^{3}H]histidine
Stoichiometry	1 Na^+ : 1 amino acid (in) : 1 H^+ (out) [388]	1 Na^+ : 1 amino acid (in) : 1 H^+ (out) [393]

Orphan SLC38 transporters

Nomenclature	SNAT6	SNAT7	–	–	PP1744	AVT2
Systematic nomenclature	SLC38A6	SLC38A7	SLC38A8	SLC38A9	SLC38A10	SLC38A11
Common abbreviation	SNAT6	SNAT7	–	–	–	–
HGNC, UniProt	*SLC38A6*, Q8IZM9	*SLC38A7*, Q9NVC3	*SLC38A8*, A6NNN8	*SLC38A9*, Q8NBW4	*SLC38A10*, Q9HBR0	*SLC38A11*, Q08AI6
Comment	–	SNAT7/SLC38A7 has been described to be a system N-like transporter allowing preferential accumulation of L-glutamine, L-histidine and L-asparagine [392]	–	–	–	–

Further reading

Bröer S, Palacín M. (2011) The role of amino acid transporters in inherited and acquired diseases. *Biochem J* **436**: 193–211. [PMID:21568940]

Hägglund MG, Sreedharan S, Nilsson VC, Shaik JH, Almkvist IM, Bäcklin S, Wrange O, Fredriksson R. (2011) Identification of SLC38A7 (SNAT7) protein as a glutamine transporter expressed in neurons. *J Biol Chem* **286**: 20500–20511. [PMID:21511949]

Mackenzie B, Erickson JD. (2004) Sodium-coupled neutral amino acid (System N/A) transporters of the SLC38 gene family. *Pflugers Arch* **447**: 784–795. [PMID:12845534]

Schiöth HB, Roshanbin S, Hägglund MG, Fredriksson R. (2013) Evolutionary origin of amino acid transporter families SLC32, SLC36 and SLC38 and physiological, pathological and therapeutic aspects. *Mol Aspects Med* **34**: 571–585. [PMID:23506890]

Sundberg BE, Wååg E, Jacobsson JA, Stephansson O, Rumaks J, Svirskis S, Alsiö J, Roman E, Ebendal T, Klusa V *et al*. (2008) The evolutionary history and tissue mapping of amino acid transporters belonging to solute carrier families SLC32, SLC36, and SLC38. *J Mol Neurosci* **35**: 179–193. [PMID:18418736]

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 [396–397].

Nomenclature	Zinc transporter 1	Zinc transporter 2	Zinc transporter 3	Zinc transporter 4	metal ion transporter 5	Zinc transporter 6	Zinc transporter 7
Systematic nomenclature	SLC39A1	SLC39A2	SLC39A3	SLC39A4	SLC39A5	SLC39A6	SLC39A7
Common abbreviation	ZIP1	ZIP2	ZIP3	ZIP4	ZIP5	ZIP6	ZIP7
HGNC, UniProt	*SLC39A1*, Q9NY26	*SLC39A2*, Q9NP94	*SLC39A3*, Q9BRY0	*SLC39A4*, Q6P5W5	*SLC39A5*, Q6ZMH5	*SLC39A6*, Q13433	*SLC39A7*, Q92504

Nomenclature	Zinc transporter 8	Zinc transporter 9	Zinc transporter 10	Zinc transporter 11	Zinc transporter 12	Zinc transporter 13	Zinc transporter 14
Systematic nomenclature	SLC39A8	SLC39A9	SLC39A10	SLC39A11	SLC39A12	SLC39A13	SLC39A14
Common abbreviation	ZIP8	ZIP9	ZIP10	ZIP11	ZIP12	ZIP13	ZIP14
HGNC, UniProt	*SLC39A8*, Q9C0K1	*SLC39A9*, Q9NUM3	*SLC39A10*, Q9ULF5	*SLC39A11*, Q8N1S5	*SLC39A12*, Q504Y0	*SLC39A13*, Q96H72	*SLC39A14*, Q15043
Substrates	Cd^{2+} [395,397]	–	–	–	–	–	Cd^{2+} [396], Fe^{2+} [398], Mn^{2+} [396]
Stoichiometry	1 Zn^{2+} (in) : 2 HCO_3^- (in) [397]	–	–	–	–	–	–

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 [396].

Further reading

Eide DJ. (2004) The SLC39 family of metal ion transporters. *Pflugers Arch* **447**: 796–800. [PMID:12748861]

Franz MC, Anderle P, Bürzle M, Suzuki Y, Freeman MR, Hediger MA, Kovacs G. (2013) Zinc transporters in prostate cancer. *Mol Aspects Med* **34**: 735–741. [PMID:23506906]

Himeno S, Yanagiya T, Fujishiro H. (2009) The role of zinc transporters in cadmium and manganese transport in mammalian cells. *Biochimie* **91**: 1218–1222. [PMID:19375483]

Jeong J, Eide DJ. (2013) The SLC39 family of zinc transporters. *Mol Aspects Med* **34**: 612–619. [PMID:23506894]

Rungby J. (2010) Zinc, zinc transporters and diabetes. *Diabetologia* **53**: 1549–1551. [PMID:20490449]

Thévenod F. (2010) Catch me if you can! Novel aspects of cadmium transport in mammalian cells. *Biometals* **23**: 857–875. [PMID:20204475]

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 [403], with the functional transporter potentially a dimeric arrangement [399–400].

Nomenclature	Ferroportin
Systematic nomenclature	SLC40A1
Common abbreviation	IREG1
HGNC, UniProt	*SLC40A1*, Q9NP59
Endogenous substrates	Fe^{2+}
Stoichiometry	Unknown

Comments: Hepcidin (*HAMP*, P81172), cleaved into hepcidin-25 (*HAMP*, P81172) and hepcidin-20 (*HAMP*, P81173), 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 [402], while loss-of-function mutations in man are associated with haemochromatosis [401].

Further reading

McKie AT, Barlow DJ. (2004) The SLC40 basolateral iron transporter family (IREG1/ferroportin/MTP1). *Pflugers Arch* **447**: 801–806. [PMID:12836025]

Montalbetti N, Simonin A, Kovacs G, Hediger MA. (2013) Mammalian iron transporters: families SLC11 and SLC40. *Mol Aspects Med* **34**: 270–287. [PMID:23506870]

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 [406], possibly as a result of co-expression of particular protein partners (see [407]). Topological modelling suggests 10 TM domains with cytoplasmic C- and N- termini.

Systematic nomenclature	SLC41A1	SLC41A2	SLC41A3
Common abbreviation	MgtE	–	–
HGNC, UniProt	*SLC41A1*, Q8IVJ1	*SLC41A2*, Q96JW4	*SLC41A3*, Q96GZ6
Substrates	Zn^{2+} [404], Mg^{2+} [404], Ba^{2+} [404], Cd^{2+} [404], Co^{2+} [404], Cu^{2+} [404], Fe^{2+} [404], Sr^{2+} [404]	Mg^{2+} [405], Ba^{2+} [405], Ni^{2+} [405], Co^{2+} [405], Fe^{2+} [405], Mn^{2+} [405]	–
Stoichiometry	Unknown	Unknown	Unknown

Further reading

Moomaw AS, Maguire ME. (2008) The unique nature of mg2+ channels. *Physiology (Bethesda)* **23**: 275–285. [PMID:18927203]

Payandeh J, Pfoh R, Pai EF. (2013) The structure and regulation of magnesium selective ion channels. *Biochim Biophys Acta* [Epub ahead of print]. [PMID:23954807]

Quamme GA. (2010) Molecular identification of ancient and modern mammalian magnesium transporters. *Am J Physiol, Cell Physiol* **298**: C407–C429. [PMID:19940067]

Sahni J, Scharenberg AM. (2013) The SLC41 family of MgtE-like magnesium transporters. *Mol Aspects Med* **34**: 620–628. [PMID:23506895]

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	RhAG	RhBG	RhCG
Systematic nomenclature	SLC42A1	SLC42A2	SLC42A3
Common abbreviation	RhAG	RhBG	RhCG
HGNC, UniProt	*RHAG*, Q02094	*RHBG*, Q9H310	*RHCG*, Q9UBD6
Substrates	NH_3 [409], NH_4^+ [410], CO_2 [408]	–	NH_3 [411]
Radioligands (K_d)	[^{14}C]methylamine	–	[^{14}C]methylamine
Stoichiometry	Unknown	Unknown	Unknown

Further reading

Huang CH, Ye M. (2010) The Rh protein family: gene evolution, membrane biology, and disease association. *Cell Mol Life Sci* **67**: 1203–1218. [PMID:19953292]

Nakhoul NL, Hamm LL. (2004) Non-erythroid Rh glycoproteins: a putative new family of mammalian ammonium transporters. *Pflugers Arch* **447**: 807–812. [PMID: 12920597]

Nakhoul NL, Lee Hamm L. (2013) Characteristics of mammalian Rh glycoproteins (SLC42 transporters) and their role in acid-base transport. *Mol Aspects Med* **34**: 629–637. [PMID:23506896]

Weiner ID, Verlander JW. (2011) Role of NH3 and NH4+ transporters in renal acid-base transport. *Am J Physiol Renal Physiol* **300**: F11–F23. [PMID:21048022]

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 [412–413]. LAT3/SLC43A1 is expressed in human tissues at high levels in the pancreas, liver, skeletal muscle and fetal liver [412] whereas LAT4/SLC43A2 is primarily expressed in the placenta, kidney and peripheral blood leukocytes [413]. SLC43A3 is expressed in vascular endothelial cells [414] but remains to be characterised.

Nomenclature	L-type amino acid transporter 3	L-type amino acid transporter 4	EEG1
Systematic nomenclature	SLC43A1	SLC43A2	SLC43A3
Common abbreviation	LAT3	LAT4	–
HGNC, UniProt	*SLC43A1*, O75387	*SLC43A2*, Q8N370	*SLC43A3*, Q8NBI5
Substrates	L-isoleucine, L-leucine, L-phenylalanine, L-valinol, L-leucinol, L-phenylalaninol, L-valine, L-methionine	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 [412] and at LAT4 inhibits the low-, but not high-affinity component of transport [413].

Further reading

Bodoy S, Fotiadis D, Stoeger C, Kanai Y, Palacín M. (2013) The small SLC43 family: facilitator system l amino acid transporters and the orphan EEG1. *Mol Aspects Med* **34**: 638–645. [PMID:23268354]

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 [423]. 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)] [420]. CLT1 is expressed almost ubiquitously in human tissues [425] and mediates choline transport across the plasma and mitochondrial membranes [419]. Transport of choline by CTL2, which in rodents is expressed as two isoforms (CTL2P1 and CLTP2; [417]) in lung, colon, inner ear and spleen and to a lesser extent in brain, tongue, liver, and kidney, has only recently been demonstrated [417,422]. CTL3-5 remain to be characterized functionally.

Nomenclature	Choline transporter-like 1	Choline transporter-like 2	Choline transporter-like 3	Choline transporter-like 4	Choline transporter-like 5
Systematic nomenclature	SLC44A1	SLC44A2	SLC44A3	SLC44A4	SLC44A5
Common abbreviation	CTL1	CTL2	CTL3	CTL4	CTL5
HGNC, UniProt	*SLC44A1*, Q8WWI5	*SLC44A2*, Q8IWA5	*SLC44A3*, Q8N4M1	*SLC44A4*, Q53GD3	*SLC44A5*, Q8NCS7
Substrates	choline	choline	–	–	–
Inhibitors (pIC_{50})	hemicholinium-3 (pK_i 3.5 – 4.5)	–	–	–	–
Stoichiometry	Unknown: uptake enhanced in the absence of extracellular Na^+, reduced by membrane depolarization, extracellular acidification and collapse of plasma membrane H^+ electrochemical gradient	–	–	–	–

Comments: Data tabulated are features observed for CLT1 endogenous to: rat astrocytes [416]; rat renal tubule epithelial cells [426]; human colon carcinoma cells [418]; human keratinocytes [424] and human neuroblastoma cells [427]. Choline uptake by CLT1 is inhibited by numerous organic cations (*e.g.* [416,426–427]). In the guinea-pig, CTL2 is a target for antibody-induced hearing loss [421] and in man, a polymorphism in CTL2 constitutes the human neutrophil alloantigen-3a (HNA-3a; [415]).

Further reading

Lockman PR, Allen DD. (2002) The transport of choline. *Drug Dev Ind Pharm* **28**: 749–771. [PMID:12236062]

Michel V, Yuan Z, Ramsubir S, Bakovic M. (2006) Choline transport for phospholipid synthesis. *Exp Biol Med (Maywood)* **231**: 490–504. [PMID:16636297]

Traiffort E, O'Regan S, Ruat M. (2013) The choline transporter-like family SLC44: properties and roles in human diseases. *Mol Aspects Med* **34**: 646–654. [PMID:23506897]

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 [430]. 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.* [429]), and polymorphisms in this gene are associated with variations in skin and hair color (*e.g.* [428]).

Systematic nomenclature	SLC45A1	SLC45A2	SLC45A3	SLC45A4
HGNC, UniProt	*SLC45A1*, Q9Y2W3	*SLC45A2*, Q9UMX9	*SLC45A3*, Q96JT2	*SLC45A4*, Q5BKX6
Substrates	L-glucose (Rat) [430], Galactose (Rat) [430]	–	–	–
Stoichiometry	Unknown; increased at acid pH [430].	–	–	–

Further reading

Vitavska O, Wieczorek H. (2013) The SLC45 gene family of putative sugar transporters. *Mol Aspects Med* **34**: 655–660. [PMID:23506898]

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 [432], 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	Thymic stromal co-transporter	–
Systematic nomenclature	SLC46A1	SLC46A2	SLC46A3
Common abbreviation	PCFT	TSCOT	–
HGNC, UniProt	*SLC46A1*, Q96NT5	*SLC46A2*, Q9BY10	*SLC46A3*, Q7Z3Q1
Substrates	folic acid (1.3μM) > heme (>100 μM) [431]	–	–
Endogenous substrates	N^5-methyltetrafolate [432]	–	–
Substrates	methotrexate [432], N-formyltetrahydrofolate, pemetrexed	–	–
Radioligands (K_d)	[^{3}H]folic acid, [^{3}H]folinic acid, [^{3}H]methotrexate, [^{3}H]N^5-methylfolate, [^{3}H]pemetrexed	–	–
Comment	Loss-of-function mutations in PCFT (SLC46A1) are the molecular basis for hereditary folate maladsorption [433]	Function as-yet unknown	Function as-yet unknown

Further reading

Anderson CM, Thwaites DT. (2010) Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* **25**: 364–377. [PMID:21186281]

Desmoulin SK, Hou Z, Gangjee A, Matherly LH. (2012) The human proton-coupled folate transporter: Biology and therapeutic applications to cancer. *Cancer Biol Ther* **13**: 1355–1373. [PMID:22954694]

Thwaites DT, Anderson CM. (2007) H+-coupled nutrient, micronutrient and drug transporters in the mammalian small intestine. *Exp Physiol* **92**: 603–619. [PMID:17468205]

Zhao R, Diop-Bove N, Visentin M, Goldman ID. (2011) Mechanisms of membrane transport of folates into cells and across epithelia. *Annu Rev Nutr* **31**: 177–201. [PMID:21568705]

Zhao R, Goldman ID. (2013) Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors. *Mol Aspects Med* **34**: 373–385. [PMID:23506878]

SLC47 family of multidrug and toxin extrusion transporters

Overview: These proton:organic cation exchangers are predicted to have 13 TM segments [443] and are suggested to be responsible for excretion of many drugs in the liver and kidneys.

Nomenclature	Multi antimicrobial extrusion protein	MATE2
Systematic nomenclature	SLC47A1	SLC47A2
Common abbreviation	MATE1	MATE2-K
HGNC, UniProt	*SLC47A1*, Q96FL8	*SLC47A2*, Q86VL8
Endogenous substrates	creatine [439], thiamine [439]	creatine [439], thiamine [439]
Substrates	cimetidine [437], quinidine [439], paraquat [434], cephradine [439], cephalexin [439]	cimetidine [436], MPP^+ [436], N^1-methylnicotinamide [436], metformin [436], guanidine [439], procainamide [436], acyclovir [439]
(Sub)family-selective inhibitors (pIC_{50})	pyrimethamine (pK_i 6.8), cimetidine (pK_i 6.0) [441]	pyrimethamine (pK_i 6.3 - Mouse) [435], cimetidine (pK_i 5.1) [441]
Radioligands (K_d)	[^{14}C]metformin [439–440], [^{14}C]TEA [438,440]	[^{14}C]TEA [439]

Comments: DAPI has been used to allow quantification of MATE1 and MATE2-mediated transport activity [442]. MATE2 and MATE2-B are inactive splice variants of MATE2-K [436].

Further reading

Damme K, Nies AT, Schaeffeler E, Schwab M. (2011) Mammalian MATE (SLC47A) transport proteins: impact on efflux of endogenous substrates and xenobiotics. *Drug Metab Rev* **43**: 499–523. [PMID:21923552]

Motohashi H, Inui K. (2013) Multidrug and toxin extrusion family SLC47: physiological, pharmacokinetic and toxicokinetic importance of MATE1 and MATE2-K. *Mol Aspects Med* **34**: 661–668. [PMID:23506899]

Terada T, Inui K. (2008) Physiological and pharmacokinetic roles of H+/organic cation antiporters (MATE/SLC47A). *Biochem Pharmacol* **75**: 1689–1696. [PMID:18262170]

Yonezawa A, Inui K. (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. *Br J Pharmacol* **164**: 1817–1825. [PMID:21457222]

SLC48 heme transporter

Overview: HRG1 has been identified as a cell surface and lysosomal heme transporter [445]. In addition, evidence suggests this 4TM-containing protein associates with the V-ATPase in lysosomes [444]. 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 [446].

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

Further reading

Khan AA, Quigley JG. (2013) Heme and FLVCR-related transporter families SLC48 and SLC49. *Mol Aspects Med* **34**: 669–682. [PMID:23506900]

SLC49 family of FLVCR-related heme transporters

Overview: FLVCR1 was initially identified as a cell-surface attachment site for feline leukemia virus subgroup C [455], and later identified as a cell surface accumulation which exports heme from the cytosol [452]. 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 [448]. 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) [453].There are three paralogs of FLVCR1 in the human genome.

FLVCR2, most similar to FLVCR1 [450], has been reported to function as a heme importer [449]. 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 [451].

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 [447].

Nomenclature	Feline leukemia virus subgroup C cellular receptor family, member 1	Feline leukemia virus subgroup C cellular receptor family, member 2	Major facilitator superfamily domain containing 7	Disrupted in renal carcinoma 2
Systematic nomenclature	SLC49A1	SLC49A2	SLC49A3	SLC49A4
Common abbreviation	FLVCR1	FLVCR2	MFSD7	DIRC2
HGNC, UniProt	*FLVCR1*, Q9Y5Y0	*FLVCR2*, Q9UPI3	*MFSD7*, Q6UXD7	*DIRC2*, Q96SL1
Substrates	heme [452]	heme [449]	–	–
Stoichiometry	Unknown	Unknown	Unknown	Unknown

Comments: Non-functional splice alternatives of FLVCR1 have been implicated as a cause of a congenital red cell aplasia, Diamond Blackfan anemia [454].

Further reading

Khan AA, Quigley JG. (2011) Control of intracellular heme levels: heme transporters and heme oxygenases. *Biochim Biophys Acta* **1813**: 668–682. [PMID:21238504]

Khan AA, Quigley JG. (2013) Heme and FLVCR-related transporter families SLC48 and SLC49. *Mol Aspects Med* **34**: 669–682. [PMID:23506900]

Krishnamurthy P, Xie T, Schuetz JD. (2007) The role of transporters in cellular heme and porphyrin homeostasis. *Pharmacol Ther* **114**: 345–358. [PMID:17368550]

Latunde-Dada GO, Simpson RJ, McKie AT. (2006) Recent advances in mammalian haem transport. *Trends Biochem Sci* **31**: 182–188. [PMID:16487711]

SLC50 sugar transporter

Overview: A mouse stromal cell cDNA library was used to clone C2.3 [457], 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 [456]. Expression of mouse SWEET in the mammary gland was suggestive of a role in Golgi lactose synthesis [456].

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

Further reading

Wright EM. (2013) Glucose transport families SLC5 and SLC50. *Mol Aspects Med* **34**: 183–196. [PMID:23506865]

Wright EM, Loo DD, Hirayama BA. (2011) Biology of human sodium glucose transporters. *Physiol Rev* **91**: 733–794. [PMID:21527736]

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 bile duct, small intestine and kidney, and elsewhere, as part of the enterohepatic circulation [458,460]. OSTα/OSTβ is also expressed in steroidogenic cells of the brain and adrenal gland, where it may contribute to steroid movement [461]. Bile acid transport is suggested to be facilitative and independent of sodium, potassium, chloride ions or protons [458,460]. OSTα/OSTβ heterodimers have been shown to transport [^{3}H]taurocholic acid, [^{3}H]DHEAS, [^{3}H]estrone-3-sulphate, [^{3}H]-pregnenolone sulphate and [^{3}H]DHEAS [458,460–461]. OSTα is suggested to be a seven TM protein, while OSTβ is a single TM 'ancillary' protein, both of which are thought to have intracellular C-termini [462]. Bimolecular fluorescence complementation studies suggest the possibility of OSTα homo-oligomers, as well as OSTα/OSTβ hetero-oligomers [459,462].

Nomenclature	OSTα	OSTβ
Systematic nomenclature	SLC51A1	SLC51A1BP
HGNC, UniProt	*SLC51A*, Q86UW1	*SLC51B*, Q86UW2

Further reading

Ballatori N. (2011) Pleiotropic functions of the organic solute transporter Ostα-Ostβ. *Dig Dis* **29**: 13–17. [PMID:21691099]

Ballatori N, Christian WV, Wheeler SG, Hammond CL. (2013) The heteromeric organic solute transporter, OSTα-OSTβ/SLC51: a transporter for steroid-derived molecules. *Mol Aspects Med* **34**: 683–692. [PMID:23506901]

Dawson PA. (2011) Role of the intestinal bile acid transporters in bile acid and drug disposition. *Handb Exp Pharmacol* (**201**): 169–203. [PMID:21103970]

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 (riboflavin transporter), member 1	solute carrier family 52 (riboflavin transporter), member 2	solute carrier family 52 (riboflavin transporter), member 3
Systematic nomenclature	SLC52A1	SLC52A2	SLC52A3
Common abbreviation	RFVT1	RFVT2	RFVT3
HGNC, UniProt	*SLC52A1*, Q9NWF4	*SLC52A2*, Q9HAB3	*SLC52A3*, Q9NQ40
Endogenous substrates	riboflavin (Km 1.38x10^{-9} M) [463]	riboflavin (Km 9.8x10^{-10} M) [463]	riboflavin (Km 3.3x10^{-10} M) [463]
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

Yamamoto S, Inoue K, Ohta KY, Fukatsu R, Maeda JY, Yoshida Y, Yuasa H. (2009) Identification and functional characterization of rat riboflavin transporter 2. *J Biochem* **145**: 437–443. [PMID:19122205]

Yonezawa A, Inui K. (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]

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
Endogenous substrates	PGE_2, bilirubin, bile acids, steroid conjugates, thyroid hormones	bilirubin, bile acids, leukotrienes, steroid conjugates, thyroid hormones	CCK-8, LTC_4, bilirubin, bile acids, steroid conjugates, thyroid hormones	steroid conjugates, thyroid hormones
Substrates	deltorphin II, rosuvastatin, BSP, talinolol, microcystin, fexofenadine, ouabain, antibiotics, anticancer drugs, beta blockers, fluoroquinolones, HIV protease inhibitors	rifampicin, BSP, fexofenadine, ACE inhibitors, anticancer drugs, antifungals, β-lactam antibiotics, bile acid derivatives and conjugates, endothelin receptor antagonists, HIV protease inhibitors, opioids, sartans, statins	erythromycin-A, rifampicin, BSP, amanitin, digoxin, phalloidin, saquinavir, fexofenadine, ouabain, anticancer drugs, β-lactam antibiotics, bile acid derivatives and conjugates, opioids, sartans, statins	BSP, statins
Inhibitors (pIC_{50})	naringin, rifampicin, rifamycin SV	cyclosporin A, gemfibrozil, glycyrrhizin, indocyanine Green, rifampicin, rifamycin SV, sildenafil	cyclosporin A, gemfibrozil, glycyrrhizin, rifampicin, rifamycin SV, sildenafil	DPDPE, probenecid, taurocholic acid
Radioligands (K_d)	[^{3}H]BSP, [^{3}H]DPDPE, [^{3}H]estrone-3-sulphate	[^{3}H]estradiol-17β-glucuronide, [^{3}H]estrone-3-sulphate	[^{3}H]BSP, [^{3}H]CCK-8 (human, mouse, rat), [^{3}H]estradiol-17β-glucuronide	[^{125}I]thyroxine, [^{3}H]BSP, [^{3}H]estrone-3-sulphate
Comment	–	Other inhibitors include fibrates, flavonoids, glitazones and macrolide antibiotics. pravastatin is used as a probe	Other inhibitors include HIV protease inhibitors, glitazones and macrolide antibiotics	–

Nomenclature	OATP2A1	OATP2B1	OATP3A1
Systematic nomenclature	SLCO2A1	SLCO2B1	SLCO3A1
HGNC, UniProt	*SLCO2A1*, Q92959	*SLCO2B1*, O94956	*SLCO3A1*, Q9UIG8
Endogenous substrates	eicosanoids, prostaglandins	T_4, dehydroepiandrosterone sulphate, estrone-3-sulphate	BQ123, vasopressin, prostaglandins, thyroid hormones
Substrates	synthetic prostaglandin derivatives	telmisartan, glibenclamide, amiodarone, bosentan, BSP, talinolol, aliskiren, fexofenadine, statins	–
Inhibitors (pIC_{50})	bromocresol green, BSP	gemfibrozil, glibenclamide, rifamycin SV	–
Radioligands (K_d)	[^{3}H]PGE_2	[^{3}H]BSP, [^{3}H]estrone-3-sulphate	[^{3}H]estrone-3-sulphate, [^{3}H]PGE_2
Comment	Other inhibitors include NSAIDs	Other inhibitors include glitazones and citrus juices	–

Nomenclature	OATP4A1	OATP4C1	OATP5A1	OATP6A1
Systematic nomenclature	SLCO4A1	SLCO4C1	SLCO5A1	SLCO6A1
HGNC, UniProt	*SLCO4A1*, Q96BD0	*SLCO4C1*, Q6ZQN7	*SLCO5A1*, Q9H2Y9	*SLCO6A1*, Q86UG4
Endogenous substrates	bile acids, prostaglandins, steroid conjugates, thyroid hormones	cAMP, steroid conjugates, thyroid hormones	–	–
Substrates	penicillin G	anticancer drugs, cardiac glycosides, dipeptidyl peptidase-4 inhibitors	–	–
Radioligands (K_d)	[^{3}H]estrone-3-sulphate	[^{3}H]digoxin	–	–

Further reading

Hagenbuch B. (2010) Drug uptake systems in liver and kidney: a historic perspective. *Clin Pharmacol Ther* **87**: 39–47. [PMID:19924123]

Hagenbuch B, Meier PJ. (2004) Organic anion transporting polypeptides of the OATP/ SLC21 family: phylogenetic classification as OATP/ SLCO superfamily, new nomenclature and molecular/ functional properties. *Pflugers Arch* **447**: 653–665. [PMID:14579113]

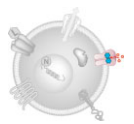
König J. (2011) Uptake transporters of the human OATP family: molecular characteristics, substrates, their role in drug-drug interactions, and functional consequences of polymorphisms. *Handb Exp Pharmacol* (**201**): 1–28. [PMID:21103967]

Niemi M, Pasanen MK, Neuvonen PJ. (2011) Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev* **63**: 157–181. [PMID:21245207]

References

1. Bakos E, Homolya L. (2007) *Pflugers Arch* **453**: 621–641. [PMID:17187268]
2. Borst P *et al*. (2007) *Pflugers Arch* **453**: 661–673. [PMID:16586096]
3. Chen ZQ *et al*. (2006) *J Biol Chem* **281**: 7452–7457. [PMID:16421098]
4. Elliott AM, Al-Hajj MA. (2009) *Mol Cancer Res* **7**: 79–87. [PMID:19147539]
5. Helias V *et al*. (2012) *Nat Genet* **44**: 170–173. [PMID:22246506]
6. Hollingworth P *et al*. (2011) *Nat Genet* **43**: 429–435. [PMID:21460840]
7. Kamakura A *et al*. (2008) *Biochem Biophys Res Commun* **377**: 847–851. [PMID:18952056]
8. Kashiwayama Y *et al*. (2009) *Exp Cell Res* **315**: 190–205. [PMID:19010322]
9. Kemp S *et al*. (2011) *Br J Pharmacol* **164**: 1753–1766. [PMID:21488864]
10. Kerr ID *et al*. (2011) *Br J Pharmacol* **164**: 1767–1779. [PMID:21175590]
11. Krishnamurthy PC *et al*. (2006) *Nature* **443**: 586–589. [PMID:17006453]
12. Leier I *et al*. (1994) *J Biol Chem* **269**: 27807–27810. [PMID:7961706]
13. Oude Elferink RP, Paulusma CC. (2007) *Pflugers Arch* **453**: 601–610. [PMID:16622704]
14. Paytubi S *et al*. (2009) *J Biol Chem* **284**: 24061–24073. [PMID:19570978]
15. Pondarre C *et al*. (2007) *Blood* **109**: 3567–3569. [PMID:17192398]
16. Reid G *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 9244–9249. [PMID:12835412]
17. Schatton T *et al*. (2008) *Nature* **451**: 345–349. [PMID:18202660]
18. Shintre CA *et al*. (2013) *Proc Natl Acad Sci USA* **110**: 9710–9715. [PMID:23716676]
19. Stieger B. (2009) *Curr Opin Lipidol* **20**: 176–181. [PMID:19684528]
20. Suzuki H, Sugiyama Y. (1998) *Semin Liver Dis* **18**: 359–376. [PMID:9875554]
21. van Roermund CW *et al*. (2008) *FASEB J* **22**: 4201–4208. [PMID:18757502]
22. van Roermund CW *et al*. (2011) *Biochim Biophys Acta* **1811**: 148–152. [PMID:21145416]
23. Zuo Y *et al*. (2008) *J Biol Chem* **283**: 36624–36635. [PMID:18957418]
24. Bagrov AY *et al*. (2009) *Pharmacol Rev* **61**: 9–38. [PMID:19325075]
25. Chong X, Rahimtula AD. (1992) *Biochem Pharmacol* **44**: 1401–1409. [PMID:1417961]
26. Hu Z *et al*. (2000) *Nat Genet* **24**: 61–65. [PMID:10615129]
27. Lytton J *et al*. (1991) *J Biol Chem* **266**: 17067–17071. [PMID:1832668]
28. Pestov NB *et al*. (2006) *Am J Physiol, Cell Physiol* **291**: C366–C374. [PMID:16525125]
29. Seidler NW *et al*. (1989) *J Biol Chem* **264**: 17816–17823. [PMID:2530215]
30. Tóth A *et al*. (2002) *Biochem Biophys Res Commun* **293**: 777–782. [PMID:12054538]
31. Amara SG, Arriza JL. (1993) *Curr Opin Neurobiol* **3**: 337–344. [PMID:8103691]
32. Apricò K *et al*. (2004) *J Neurosci Res* **75**: 751–759. [PMID:14994336]
33. Apricò K *et al*. (2007) *Neurochem Int* **51**: 507–516. [PMID:17590480]
34. Apricó K *et al*. (2001) *J Neurochem* **77**: 1218–1225. [PMID:11389172]
35. Arriza JL *et al*. (1993) *J Biol Chem* **268**: 15329–15332. [PMID:8101838]
36. Bailey CG *et al*. (2011) *J Clin Invest* **121**: 446–453. [PMID:21123949]
37. Beart PM, O'Shea RD. (2007) *Br J Pharmacol* **150**: 5–17. [PMID:17088867]
38. Boudker O *et al*. (2007) *Nature* **445**: 387–393. [PMID:17230192]
39. Bröer A *et al*. (1999) *J Neurochem* **73**: 2184–2194. [PMID:10537079]
40. Bröer A *et al*. (2000) *Biochem J* **346 Pt 3**: 705–710. [PMID:10698697]
41. Colleoni S *et al*. (2008) *J Pharmacol Exp Ther* **326**: 646–656. [PMID:18451317]
42. Colton CK *et al*. (2010) *J Biomol Screen* **15**: 653–662. [PMID:20508255]
43. Coon, TR *et al*. (2004) Abstract Viewer/Itinerary Planner, Program No. 168.10. *in* Society for Neuroscience.
44. Dunlop J. (2006) *Curr Opin Pharmacol* **6**: 103–107. [PMID:16368269]
45. Dunlop J *et al*. (2003) *Br J Pharmacol* **140**: 839–846. [PMID:14517179]
46. Dunlop J *et al*. (2005) *Mol Pharmacol* **68**: 974–982. [PMID:16014807]
47. Eliasof S *et al*. (2001) *J Neurochem* **77**: 550–557. [PMID:11299317]
48. Esslinger CS *et al*. (2005) *Neuropharmacology* **49**: 850–861. [PMID:16183084]
49. Esslinger CS *et al*. (2005) *Bioorg Med Chem* **13**: 1111–1118. [PMID:15670919]
50. Fontana AC *et al*. (2007) *Mol Pharmacol* **72**: 1228–1237. [PMID:17646426]
51. Fontana AC *et al*. (2003) *Br J Pharmacol* **139**: 1297–1309. [PMID:12890709]
52. Gameiro A *et al*. (2011) *Biophys J* **100**: 2623–2632. [PMID:21641307]
53. Ganel R *et al*. (2006) *Neurobiol Dis* **21**: 556–567. [PMID:16274998]
54. Gebhardt FM *et al*. (2010) *J Biol Chem* **285**: 31313–31324. [PMID:20688910]
55. Gendreau S *et al*. (2004) *J Biol Chem* **279**: 39505–39512. [PMID:15265858]
56. Goursaud S *et al*. (2011) *FASEB J* **25**: 3674–3686. [PMID:21730107]
57. Grewer C *et al*. (2005) *Biochemistry* **44**: 11913–11923. [PMID:16128593]
58. Grewer C, Grabsch E. (2004) *J Physiol (Lond)* **557** (Pt 3): 747–759. [PMID:15107471]
59. Grewer C, Rauen T. (2005) *J Membr Biol* **203**: 1–20. [PMID:15834685]
60. Grunewald M, Kanner BI. (2000) *J Biol Chem* **275**: 9684–9689. [PMID:10734120]
61. Huang S *et al*. (2009) *J Biol Chem* **284**: 4510–4515. [PMID:19074430]
62. Jensen AA *et al*. (2009) *J Med Chem* **52**: 912–915. [PMID:19161278]
63. Jiang J, Amara SG. (2011) *Neuropharmacology* **60**: 172–181. [PMID:20708631]
64. Kanai Y, Hediger MA. (2003) *Eur J Pharmacol* **479**: 237–247. [PMID:14612154]
65. Kanai Y, Hediger MA. (2004) *Pflugers Arch* **447**: 469–479. [PMID:14530974]
66. Kim K *et al*. (2011) *J Cell Physiol* **226**: 2484–2493. [PMID:21792905]
67. Koch HP *et al*. (2007) *J Neurosci* **27**: 2943–2947. [PMID:17360917]
68. Lau CL *et al*. (2011) *Br J Pharmacol* **163**: 533–545. [PMID:21309758]
69. Leary GP *et al*. (2007) *J Neurosci* **27**: 2938–2942. [PMID:17360916]
70. Lee A, Pow DV. (2010) *Int J Biochem Cell Biol* **42**: 1901–1906. [PMID:20883814]
71. Lee SG *et al*. (2008) *J Biol Chem* **283**: 13116–13123. [PMID:18326497]
72. Levy LM *et al*. (1998) *J Neurosci* **18**: 9620–9628. [PMID:9822723]
73. Machtens JP *et al*. (2011) *J Biol Chem* **286**: 23780–23788. [PMID:21572047]
74. Nothmann D *et al*. (2011) *J Biol Chem* **286**: 3935–3943. [PMID:21127051]
75. Oppedisano F *et al*. (2010) *Biochem Pharmacol* **80**: 1266–1273. [PMID:20599776]
76. Palacín M *et al*. (1998) *Physiol Rev* **78**: 969–1054. [PMID:9790568]
77. Pinilla-Tenas J *et al*. (2003) *J Membr Biol* **195**: 27–32. [PMID:14502423]
78. Reyes N *et al*. (2009) *Nature* **462**: 880–885. [PMID:19924125]
79. Romera C *et al*. (2007) *J Cereb Blood Flow Metab* **27**: 1327–1338. [PMID:17213861]
80. Rose EM *et al*. (2009) *J Neurosci* **29**: 8143–8155. [PMID:19553454]
81. Rothstein JD *et al*. (2005) *Nature* **433**: 73–77. [PMID:15635412]
82. Ryan RM, Mindell JA. (2007) *Nat Struct Mol Biol* **14**: 365–371. [PMID:17435767]
83. Ryan RM *et al*. (2004) *J Biol Chem* **279**: 20742–20751. [PMID:14982939]
84. Shigeri Y *et al*. (2001) *J Neurochem* **79**: 297–302. [PMID:11677257]
85. Shimamoto K *et al*. (1998) *Mol Pharmacol* **53**: 195–201. [PMID:9463476]
86. Shimamoto K *et al*. (2007) *Mol Pharmacol* **71**: 294–302. [PMID:17047096]
87. Tamarappoo BK *et al*. (1996) *Biochim Biophys Acta* **1279**: 131–136. [PMID:8603078]
88. Torres-Salazar D, Fahlke C. (2007) *J Biol Chem* **282**: 34719–34726. [PMID:17908688]
89. Utsunomiya-Tate N *et al*. (1996) *J Biol Chem* **271**: 14883–14890. [PMID:8662767]
90. Vandenberg RJ *et al*. (2004) *Eur J Pharm Sci* **23**: 1–11. [PMID:15324920]
91. Vandenberg RJ *et al*. (1997) *Mol Pharmacol* **51**: 809–815. [PMID:9145919]
92. Veruki ML *et al*. (2006) *Nat Neurosci* **9**: 1388–1396. [PMID:17041592]
93. Yernool D *et al*. (2004) *Nature* **431**: 811–818. [PMID:15483603]

94. Zerangue N, Kavanaugh MP. (1996) *J Physiol (Lond)* **493 (Pt 2)**: 419–423. [PMID:8782106]
95. Zerangue N, Kavanaugh MP. (1996) *Nature* **383**: 634–637. [PMID:8857541]
96. Zerangue N, Kavanaugh MP. (1996) *J Biol Chem* **271**: 27991–27994. [PMID:8910405]
97. Zhou LM *et al*. (1997) *J Pharmacol Exp Ther* **280**: 422–427. [PMID:8996224]
98. Zou S *et al*. (2011) *J Neurochem* **117**: 833–840. [PMID:21426345]
99. Bianchi J, Rose RC. (1986) *Proc Soc Exp Biol Med* **181**: 333–337. [PMID:3945643]
100. Di Daniel E *et al*. (2009) *BMC Cell Biol* **10**: 54. [PMID:19607714]
101. Ibberson M *et al*. (2000) *J Biol Chem* **275**: 4607–4612. [PMID:10671487]
102. Lee YC *et al*. (2010) *Hum Mol Genet* **19**: 3721–3733. [PMID:20639396]
103. Rogers S *et al*. (2003) *Biochem Biophys Res Commun* **308**: 422–426. [PMID:12914765]
104. Uldry M *et al*. (2002) *FEBS Lett* **524**: 199–203. [PMID:12135767]
105. Wu X, Freeze HH. (2002) *Genomics* **80**: 553–557. [PMID:12504846]
106. Wolf S *et al*. (2002) *Biochem J* **364** (Pt 3): 767–775. [PMID:12049641]
107. Abramson J, Wright EM. (2009) *Curr Opin Struct Biol* **19**: 425–432. [PMID:19631523]
108. Aouameur R *et al*. (2007) *Am J Physiol Gastrointest Liver Physiol* **293**: G1300-G1307. [PMID:17932225]
109. Apparsundaram S *et al*. (2000) *Biochem Biophys Res Commun* **276**: 862–867. [PMID:11027560]
110. Bissonnette P *et al*. (2004) *J Physiol (Lond)* **558** (Pt 3): 759–768. [PMID:15181167]
111. Bizhanova A, Kopp P. (2009) *Endocrinology* **150**: 1084–1090. [PMID:19196800]
112. Bourgeois F *et al*. (2005) *J Physiol (Lond)* **563** (Pt 2): 333–343. [PMID:15613375]
113. Chao EC, Henry RR. (2010) *Nat Rev Drug Discov* **9**: 551–559. [PMID:20508640]
114. Coady MJ *et al*. (2007) *Biophys J* **93**: 2325–2331. [PMID:17526579]
115. Coady MJ *et al*. (2002) *J Biol Chem* **277**: 35219–35224. [PMID:12133831]
116. de Carvalho FD, Quick M. (2011) *J Biol Chem* **286**: 131–137. [PMID:20980265]
117. Diez-Sampedro A *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 11753–11758. [PMID:13130073]
118. Dohán O *et al*. (2007) *Proc Natl Acad Sci USA* **104**: 20250–20255. [PMID:18077370]
119. Eskandari S *et al*. (1997) *J Biol Chem* **272**: 27230–27238. [PMID:9341168]
120. Ferguson SM *et al*. (2004) *Proc Natl Acad Sci USA* **101**: 8762–8767. [PMID:15173594]
121. Ferguson SM, Blakely RD. (2004) *Mol Interv* **4**: 22–37. [PMID:14993474]
122. Ganapathy V *et al*. (2008) *AAPS J* **10**: 193–199. [PMID:18446519]
123. Ganapathy V *et al*. (2009) *Pharmacol Ther* **121**: 29–40. [PMID:18992769]
124. Gopal E *et al*. (2005) *Biochem J* **388** (Pt 1): 309–316. [PMID:15651982]
125. Gupta N *et al*. (2006) *Life Sci* **78**: 2419–2425. [PMID:16375929]
126. Hager K *et al*. (1995) *J Membr Biol* **143**: 103–113. [PMID:7537337]
127. Hummel CS *et al*. (2011) *Am J Physiol, Cell Physiol* **300**: C14–C21. [PMID:20980548]
128. Iwamoto H *et al*. (2006) *J Neurosci* **26**: 9851–9859. [PMID:17005849]
129. Kanai Y *et al*. (1994) *J Clin Invest* **93**: 397–404. [PMID:8282810]
130. Krishnaswamy A, Cooper E. (2009) *Neuron* **61**: 272–286. [PMID:19186169]
131. Lin X *et al*. (2009) *Arch Biochem Biophys* **481**: 197–201. [PMID:19032932]
132. Miyauchi S *et al*. (2004) *J Biol Chem* **279**: 13293–13296. [PMID:14966140]
133. Okuda T, Haga T. (2000) *FEBS Lett* **484**: 92–97. [PMID:11068039]
134. Prasad PD *et al*. (2000) *Biochem Biophys Res Commun* **270**: 836–840. [PMID:10772912]
135. Said HM. (2009) *J Nutr* **139**: 158–162. [PMID:19056639]
136. Said HM *et al*. (1989) *Am J Clin Nutr* **49**: 127–131. [PMID:2911998]
137. Singh N *et al*. (2010) *J Biol Chem* **285**: 27601–27608. [PMID:20601425]
138. Thangaraju M *et al*. (2006) *J Biol Chem* **281**: 26769–26773. [PMID:16873376]
139. Thangaraju M *et al*. (2006) *Cancer Res* **66**: 11560–11564. [PMID:17178845]
140. Traiffort E *et al*. (2005) *J Neurochem* **92**: 1116–1125. [PMID:15715662]
141. Wang H *et al*. (1999) *J Biol Chem* **274**: 14875–14883. [PMID:10329687]
142. Wright EM *et al*. (2011) *Physiol Rev* **91**: 733–794. [PMID:21527736]
143. Wright EM, Turk E. (2004) *Pflugers Arch* **447**: 510–518. [PMID:12748858]
144. Anderson CM *et al*. (2008) *J Physiol (Lond)* **586** (Pt 17): 4061–4067. [PMID:18599538]
145. Anderson CM *et al*. (2009) *J Physiol (Lond)* **587** (Pt 4): 731–744. [PMID:19074966]
146. Aubrey KR *et al*. (2000) *Mol Pharmacol* **58**: 129–135. [PMID:10860934]
147. Bergeron R *et al*. (1998) *Proc Natl Acad Sci USA* **95**: 15730–15734. [PMID:9861038]
148. Betz H *et al*. (2006) *Biochem Soc Trans* **34** (Pt 1): 55–58. [PMID:16417482]
149. Brown A *et al*. (2001) *Bioorg Med Chem Lett* **11**: 2007–2009. [PMID:11454468]
150. Bröer A *et al*. (2009) *Mol Membr Biol* **26**: 333–346. [PMID:19657969]
151. Bröer A *et al*. (2006) *Biochem J* **393** (Pt 1): 421–430. [PMID:16185194]
152. Bröer S. (2006) *Neurochem Int* **48**: 559–567. [PMID:16540203]
153. Bröer S. (2008) *Physiology (Bethesda)* **23**: 95–103. [PMID:18400692]
154. Böhmer C *et al*. (2005) *Biochem J* **389** (Pt 3): 745–751. [PMID:15804236]
155. Carland JE *et al*. (2013) *Br J Pharmacol* **168**: 891–902. [PMID:22978602]
156. Chen NH *et al*. (2004) *Pflugers Arch* **447**: 519–531. [PMID:12719981]
157. Clausen RP *et al*. (2006) *Adv Pharmacol* **54**: 265–284. [PMID:17175818]
158. Cohen-Kfir E *et al*. (2005) *Proc Natl Acad Sci USA* **102**: 6154–6159. [PMID:15829583]
159. Dai W *et al*. (1999) *Arch Biochem Biophys* **361**: 75–84. [PMID:9882430]
160. Dhar TG *et al*. (1994) *J Med Chem* **37**: 2334–2342. [PMID:8057281]
161. Dodd JR, Christie DL. (2007) *J Biol Chem* **282**: 15528–15533. [PMID:17400549]
162. Edington AR *et al*. (2009) *J Biol Chem* **284**: 36424–36430. [PMID:19875446]
163. Eulenburg V *et al*. (2005) *Trends Biochem Sci* **30**: 325–333. [PMID:15950877]
164. Forrest LR, Rudnick G. (2009) *Physiology (Bethesda)* **24**: 377–386. [PMID:19996368]
165. Fülep GH *et al*. (2006) *Eur J Med Chem* **41**: 809–824. [PMID:16766089]
166. Gabernet L *et al*. (2005) *Neurosci Lett* **373**: 79–84. [PMID:15555781]
167. Gomeza J *et al*. (2006) *Handb Exp Pharmacol* (**175**): 457–483. [PMID:16722246]
168. Gomeza J *et al*. (2003) *Neuron* **40**: 785–796. [PMID:14622582]
169. Gomeza J *et al*. (2003) *Neuron* **40**: 797–806. [PMID:14622583]
170. Gu H *et al*. (1994) *J Biol Chem* **269**: 7124–7130. [PMID:8125921]
171. Gu HH *et al*. (1996) *J Biol Chem* **271**: 6911–6916. [PMID:8636118]
172. Han X *et al*. (2006) *Acta Physiol (Oxf)* **187**: 61–73. [PMID:16734743]
173. Harvey RJ *et al*. (2008) *Trends Genet* **24**: 439–447. [PMID:18707791]
174. Hatanaka T *et al*. (2001) *J Clin Invest* **107**: 1035–1043. [PMID:11306607]
175. Jeong HJ *et al*. (2010) *Br J Pharmacol* **161**: 925–935. [PMID:20860669]
176. Ju P *et al*. (2004) *J Biol Chem* **279**: 22983–22991. [PMID:15031290]
177. Karunakaran S *et al*. (2008) *Biochem J* **414**: 343–355. [PMID:18522536]
178. Knutsen LJ *et al*. (1999) *J Med Chem* **42**: 3447–3462. [PMID:10479278]
179. Kristensen AS *et al*. (2011) *Pharmacol Rev* **63**: 585–640. [PMID:21752877]
180. Kvist T *et al*. (2009) *Comb Chem High Throughput Screen* **12**: 241–249. [PMID:19275529]
181. Madsen KK *et al*. (2010) *Pharmacol Ther* **125**: 394–401. [PMID:20026354]
182. Mallorga PJ *et al*. (2003) *Neuropharmacology* **45**: 585–593. [PMID:12941372]
183. Mezler M *et al*. (2008) *Mol Pharmacol* **74**: 1705–1715. [PMID:18815213]
184. Núñez E *et al*. (2000) *Br J Pharmacol* **129**: 200–206. [PMID:10694221]
185. Pearlman RJ *et al*. (2003) *J Neurochem* **84**: 592–601. [PMID:12558979]
186. Pristupa ZB *et al*. (1994) *Mol Pharmacol* **45**: 125–135. [PMID:8302271]
187. Pérez-Siles G *et al*. (2011) *J Neurochem* **118**: 195–204. [PMID:21574997]
188. Rousseau F *et al*. (2008) *J Neurosci* **28**: 9755–9768. [PMID:18815261]
189. Saier MH *et al*. (2009) *Nucleic Acids Res* **37** (Database issue): D274–D278. [PMID:19022853]
190. Schousboe A *et al*. (2011) *Future Med Chem* **3**: 183–187. [PMID:21428813]



191. Schousboe A *et al*. (2004) *Biochem Pharmacol* **68**: 1557–1563. [PMID:15451399]
192. Semyanov A *et al*. (2004) *Trends Neurosci* **27**: 262–269. [PMID:15111008]
193. Singer D *et al*. (2009) *J Biol Chem* **284**: 19953–19960. [PMID:19478081]
194. Singh SK *et al*. (2007) *Nature* **448**: 952–956. [PMID:17687333]
195. Sloan JL, Mager S. (1999) *J Biol Chem* **274**: 23740–23745. [PMID:10446133]
196. Supplisson S, Roux MJ. (2002) *FEBS Lett* **529**: 93–101. [PMID:12354619]
197. Talvenheimo J *et al*. (1983) *J Biol Chem* **258**: 6115–6119. [PMID:6853478]
198. Tatsumi M *et al*. (1997) *Eur J Pharmacol* **340**: 249–258. [PMID:9537821]
199. Tsai G *et al*. (2004) *Proc Natl Acad Sci USA* **101**: 8485–8490. [PMID:15159536]
200. Umapathy NS *et al*. (2004) *Pharm Res* **21**: 1303–1310. [PMID:15290873]
201. Vandenberg RJ *et al*. (2004) *Eur J Pharm Sci* **23**: 1–11. [PMID:15324920]
202. Vandenberg RJ *et al*. (2007) *J Biol Chem* **282**: 14447–14453. [PMID:17383967]
203. Vanslambrouck JM *et al*. (2010) *Biochem J* **428**: 397–407. [PMID:20377526]
204. Wiles AL *et al*. (2006) *J Neurochem* **99**: 781–786. [PMID:16899062]
205. Wong EH *et al*. (2000) *Biol Psychiatry* **47**: 818–829. [PMID:10812041]
206. Yamashita A *et al*. (2005) *Nature* **437**: 215–223. [PMID:16041361]
207. Yee BK *et al*. (2006) *J Neurosci* **26**: 3169–3181. [PMID:16554468]
208. Yu XC *et al*. (2009) *Neurosci Lett* **451**: 212–216. [PMID:19159658]
209. Zaia KA, Reimer RJ. (2009) *J Biol Chem* **284**: 8439–8448. [PMID:19147495]
210. Zhang HX *et al*. (2009) *J Physiol (Lond)* **587** (Pt 13): 3207–3220. [PMID:19433577]
211. Dong H *et al*. (2002) *Biophys J* **82**: 1943–1952. [PMID:11916852]
212. Jost N *et al*. (2013) *Br J Pharmacol* [Epub ahead of print]. [PMID:23647096]
213. Counillon L *et al*.(1993) *Mol Pharmacol* **44**: 1041–1045. [PMID:8246907]
214. Lee SH *et al*. (2008) *Biochem Biophys Res Commun* **369**: 320–326. [PMID:18269914]
215. Miyazaki E *et al*. (2001) *J Biol Chem* **276**: 49221–49227. [PMID:11641397]
216. Nakamura N *et al*. (2005) *J Biol Chem* **280**: 1561–1572. [PMID:15522866]
217. Numata M, Orlowski J. (2001) *J Biol Chem* **276**: 17387–17394. [PMID:11279194]
218. Tse CM *et al*. (1993) *Proc Natl Acad Sci USA* **90**: 9110–9114. [PMID:8415663]
219. Tse CM *et al*. (1993) *J Biol Chem* **268**: 11917–11924. [PMID:7685025]
220. Wang D *et al*. (2003) *Nat Cell Biol* **5**: 1117–1122. [PMID:14634667]
221. Banerjee A, Swaan PW. (2006) *Biochemistry* **45**: 943–953. [PMID:16411770]
222. Bhat BG *et al*. (2003) *J Lipid Res* **44**: 1614–1621. [PMID:12810816]
223. Burger S *et al*. (2011) *Neuroscience* **193**: 109–121. [PMID:21742018]
224. Craddock AL *et al*. (1998) *Am J Physiol* **274** (1 Pt 1): G157–G169. [PMID:9458785]
225. Dawson PA *et al*. (2009) *J Lipid Res* **50**: 2340–2357. [PMID:19498215]
226. Dong Z *et al*. (2013) *Mol Pharm* **10**: 1008–1019. [PMID:23339484]
227. Fernandes CF *et al*. (2007) *Biochem Biophys Res Commun* **361**: 26–32. [PMID:17632081]
228. Geyer J *et al*. (2007) *J Biol Chem* **282**: 19728–19741. [PMID:17491011]
229. Geyer J *et al*. (2008) *Neuroscience* **152**: 990–1005. [PMID:18355966]
230. Geyer J *et al*. (2004) *Biochem Biophys Res Commun* **316**: 300–306. [PMID:15020217]
231. Godoy JR *et al*. (2007) *Eur J Cell Biol* **86**: 445–460. [PMID:17628207]
232. Hallén S *et al*. (1999) *Biochemistry* **38**: 11379–11388. [PMID:10471288]
233. Kim RB *et al*. (1999) *J Pharmacol Exp Ther* **291**: 1204–1209. [PMID:10565843]
234. Klaassen CD, Aleksunes LM. (2010) *Pharmacol Rev* **62**: 1–96. [PMID:20103563]
235. Meier PJ *et al*. (1997) *Hepatology* **26**: 1667–1677. [PMID:9398014]
236. Tollefson MB *et al*. (2003) *Bioorg Med Chem Lett* **13**: 3727–3730. [PMID:14552767]
237. Visser WE *et al*. (2010) *Mol Cell Endocrinol* **315**: 138–145. [PMID:19682536]
238. Weinman SA *et al*. (1998) *J Biol Chem* **273**: 34691–34695. [PMID:9856990]
239. Wu Y *et al*. (2013) *J Med Chem* **56**: 5094–5114. [PMID:23678871]
240. Gunshin H *et al*. (1997) *Nature* **388**: 482–488. [PMID:9242408]
241. Delpire E *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 5383–5388. [PMID:19279215]
242. Hannaert P *et al*. (2002) *Naunyn Schmiedebergs Arch Pharmacol* **365**: 193–199. [PMID:11882915]
243. Ito Y *et al*. (2001) *Eur J Pharmacol* **426**: 175–178. [PMID:11527541]
244. Maciver B *et al*. (2008) *Am J Physiol Renal Physiol* **294**: F956–F964. [PMID:18256317]
245. Stewart G. (2011) *Br J Pharmacol* **164**: 1780–1792. [PMID:21449978]
246. Zhao D *et al*. (2007) *Biochim Biophys Acta* **1768**: 1815–1821. [PMID:17506977]
247. Bhardwaj RK *et al*. (2006) *Eur J Pharm Sci* **27**: 533–542. [PMID:16289537]
248. Biegel A *et al*. (2006) *Amino Acids* **31**: 137–156. [PMID:16868651]
249. Blasius AL *et al*. (2010) *Proc Natl Acad Sci USA* **107**: 19973–19978. [PMID:21045126]
250. Botka CW *et al*. (2000) *AAPS PharmSci* **2**: E16. [PMID:11741232]
251. Daniel H, Kottra G. (2004) *Pflugers Arch* **447**: 610–618. [PMID:12905028]
252. Darcel NP *et al*. (2005) *J Nutr* **135**: 1491–1495. [PMID:15930458]
253. Döring F *et al*. (1998) *J Clin Invest* **101**: 2761–2767. [PMID:9637710]
254. Ganapathy ME *et al*. (1995) *J Biol Chem* **270**: 25672–25677. [PMID:7592745]
255. Ganapathy ME *et al*. (1998) *Biochem Biophys Res Commun* **246**: 470–475. [PMID:9610386]
256. Han H *et al*. (1998) *Pharm Res* **15**: 1154–1159. [PMID:9706043]
257. Herrera-Ruiz D, Knipp GT. (2003) *J Pharm Sci* **92**: 691–714. [PMID:12661057]
258. Knütter I *et al*. (2001) *Biochemistry* **40**: 4454–4458. [PMID:11284702]
259. Lee J *et al*. (2009) *J Biol Chem* **284**: 23818–23829. [PMID:19570976]
260. Merlin D *et al*. (1998) *J Clin Invest* **102**: 2011–2018. [PMID:9835627]
261. Newstead S *et al*. (2011) *EMBO J* **30**: 417–426. [PMID:21131908]
262. Romano A *et al*. (2010) *Mol Cell Endocrinol* **315**: 174–181. [PMID:19913073]
263. Rubio-Aliaga I, Daniel H. (2008) *Xenobiotica* **38**: 1022–1042. [PMID:18668438]
264. Sakata K *et al*. (2001) *Biochem J* **356** (Pt 1): 53–60. [PMID:11336635]
265. Sasawatari S *et al*. (2011) *Gastroenterology* **140**: 1513–1525. [PMID:21277849]
266. Sun Y *et al*. (2009) *Mol Pharm* **6**: 315–325. [PMID:19115956]
267. Theis S *et al*. (2002) *Mol Pharmacol* **61**: 214–221. [PMID:11752223]
268. Vavricka SR *et al*. (2004) *Gastroenterology* **127**: 1401–1409. [PMID:15521010]
269. Watanabe K *et al*. (2002) *Biol Pharm Bull* **25**: 885–890. [PMID:12132663]
270. Friesema EC *et al*. (2006) *Mol Endocrinol* **20**: 2761–2772. [PMID:16887882]
271. Murakami Y *et al*. (2005) *Drug Metab Dispos* **33**: 1845–1851. [PMID:16174808]
272. Wang Q *et al*. (2006) *J Pharmacol Exp Ther* **318**: 751–761. [PMID:16707723]
273. Bellocchio EE *et al*. (2000) *Science* **289**: 957–960. [PMID:10938000]
274. Busch AE *et al*. (1996) *Proc Natl Acad Sci USA* **93**: 5347–5351. [PMID:8643577]
275. Iharada M *et al*. (2010) *J Biol Chem* **285**: 26107–26113. [PMID:20566650]
276. Juge N *et al*. (2010) *Neuron* **68**: 99–112. [PMID:20920794]
277. Miyaji T *et al*. (2011) *J Neurochem* **119**: 1–5. [PMID:21781115]
278. Sawada K *et al*. (2008) *Proc Natl Acad Sci USA* **105**: 5683–5686. [PMID:18375752]
279. Verheijen FW *et al*. (1999) *Nat Genet* **23**: 462–465. [PMID:10581036]
280. Bravo DT *et al*. (2004) *J Neurochem* **91**: 766–768. [PMID:15485505]
281. Bravo DT *et al*. (2005) *Neurochem Int* **47**: 243–247. [PMID:15979764]
282. Efange SM *et al*. (1995) *Biochem Pharmacol* **49**: 791–797. [PMID:7702637]
283. Eiden LE *et al*. (2004) *Pflugers Arch* **447**: 636–640. [PMID:12827358]
284. Eiden LE, Weihe E. (2011) *Ann N Y Acad Sci* **1216**: 86–98. [PMID:21272013]
285. Erickson JD, Eiden LE. (1993) *J Neurochem* **61**: 2314–2317. [PMID:8245983]
286. Erickson JD *et al*. (1996) *Proc Natl Acad Sci USA* **93**: 5166–5171. [PMID:8643547]
287. Erickson JD *et al*. (1994) *J Biol Chem* **269**: 21929–21932. [PMID:8071310]
288. Khare P *et al*. (2010) *Biochemistry* **49**: 3049–3059. [PMID:20225888]

289. Kung MP *et al.* (1994) *Synapse* **18**: 225–232. [PMID:7855735]
290. Schirmer SU *et al.* (2011) *Reproduction* **142**: 157–166. [PMID:21482687]
291. Varoqui H, Erickson JD. (1996) *J Biol Chem* **271**: 27229–27232. [PMID:8910293]
292. Zhu L *et al.* (2009) *Bioorg Med Chem Lett* **19**: 5026–5028. [PMID:19632829]
293. Assaraf YG *et al.* (1998) *J Biol Chem* **273**: 8106–8111. [PMID:9525913]
294. Diaz GA *et al.* (1999) *Nat Genet* **22**: 309–312. [PMID:10391223]
295. Dutta B *et al.* (1999) *J Biol Chem* **274**: 31925–31929. [PMID:10542220]
296. Prasad PD *et al.* (1995) *Biochem Biophys Res Commun* **206**: 681–687. [PMID:7826387]
297. Rajgopal A *et al.* (2001) *Biochim Biophys Acta* **1537**: 175–178. [PMID:11731220]
298. Zhao R *et al.* (2002) *Am J Physiol, Cell Physiol* **282**: C1512–C1517. [PMID:11997266]
299. Ravera S *et al.* (2007) *Am J Physiol, Cell Physiol* **293**: C606–C620. [PMID:17494632]
300. Cha SH *et al.* (2000) *J Biol Chem* **275**: 4507–4512. [PMID:10660625]
301. Enomoto A *et al.* (2002) *Nature* **417**: 447–452. [PMID:12024214]
302. Gorboulev V *et al.* (1997) *DNA Cell Biol* **16**: 871–881. [PMID:9260930]
303. Gründemann D *et al.* (1999) *Mol Pharmacol* **56**: 1–10. [PMID:10385678]
304. Kimura H *et al.* (2002) *J Pharmacol Exp Ther* **301**: 293–298. [PMID:11907186]
305. Kusuhara H *et al.* (1999) *J Biol Chem* **274**: 13675–13680. [PMID:10224140]
306. Youngblood GL, Sweet DH. (2004) *Am J Physiol Renal Physiol* **287**: F236–F244. [PMID:15068970]
307. Zhu HJ *et al.* (2010) *J Neurochem* **114**: 142–149. [PMID:20402963]
308. Tsukaguchi H *et al.* (1999) *Nature* **399**: 70–75. [PMID:10331392]
309. Yamamoto S *et al.* (2010) *J Biol Chem* **285**: 6522–6531. [PMID:20042597]
310. Altimimi HF, Schnetkamp PP. (2007) *Channels (Austin)* **1**: 62–69. [PMID:18690016]
311. Fiermonte G *et al.* (2003) *J Biol Chem* **278**: 32778–32783. [PMID:12807890]
312. Fiermonte G *et al.* (2009) *J Biol Chem* **284**: 18152–18159. [PMID:19429682]
313. Chang MH *et al.* (2009) *J Membr Biol* **228**: 125–140. [PMID:19365592]
314. Dorwart MR *et al.* (2007) *J Physiol (Lond)* **584** (Pt 1): 333–345. [PMID:17673510]
315. Kim KH *et al.* (2005) *J Biol Chem* **280**: 6463–6470. [PMID:15591059]
316. Blackburn C *et al.* (2006) *Bioorg Med Chem Lett* **16**: 3504–3509. [PMID:16644217]
317. Faergeman NJ *et al.* (1997) *J Biol Chem* **272**: 8531–8538. [PMID:9079682]
318. Gimeno RE *et al.* (2003) *J Biol Chem* **278**: 16039–16044. [PMID:12556534]
319. Lewis SE *et al.* (2001) *J Biol Chem* **276**: 37042–37050. [PMID:11470793]
320. Li H *et al.* (2008) *J Lipid Res* **49**: 230–244. [PMID:17928635]
321. Mihalik SJ *et al.* (2002) *J Biol Chem* **277**: 24771–24779. [PMID:11980911]
322. Milger K *et al.* (2006) *J Cell Sci* **119** (Pt 22): 4678–4688. [PMID:17062637]
323. Ordovás L *et al.* (2006) *Cytogenet Genome Res* **115**: 115–122. [PMID:17065791]
324. Sandoval A *et al.* (2010) *Biochem Pharmacol* **79**: 990–999. [PMID:19913517]
325. Schaffer JE, Lodish HF. (1994) *Cell* **79**: 427–436. [PMID:7954810]
326. Stahl A *et al.* (1999) *Mol Cell* **4**: 299–308. [PMID:10518211]
327. Zhou W *et al.* (2010) *J Biomol Screen* **15**: 488–497. [PMID:20448275]
328. Baldwin SA *et al.* (2005) *J Biol Chem* **280**: 15880–15887. [PMID:15701636]
329. Engel K, Wang J. (2005) *Mol Pharmacol* **68**: 1397–1407. [PMID:16099839]
330. Hammond JR, Archer RG. (2004) *J Pharmacol Exp Ther* **308**: 1083–1093. [PMID:14634039]
331. Hsu CL *et al.* (2012) *Science* **335**: 89–92. [PMID:22174130]
332. Kang N *et al.* (2010) *J Biol Chem* **285**: 28343–28352. [PMID:20595384]
333. Sundaram M *et al.* (1998) *J Biol Chem* **273**: 21519–21525. [PMID:9705281]
334. Warraich S *et al.* (2013) *J Bone Miner Res* **28**: 1135–1149. [PMID:23184610]
335. Yao SY *et al.* (2011) *J Biol Chem* **286**: 32552–32562. [PMID:21795683]
336. Salazar G *et al.* (2009) *PLoS ONE* **4**: e5896. [ePMID:19521526]
337. Suzuki T *et al.* (2005) *J Biol Chem* **280**: 30956–30962. [PMID:15994300]
338. Blair BG *et al.* (2009) *Clin Cancer Res* **15**: 4312–4321. [PMID:19509135]
339. Ishida S *et al.* (2002) *Proc Natl Acad Sci USA* **99**: 14298–14302. [PMID:12370430]
340. Lee J *et al.* (2002) *J Biol Chem* **277**: 4380–4387. [PMID:11734551]
341. Rees EM *et al.* (2004) *J Biol Chem* **279**: 54221–54229. [PMID:15494390]
342. Fattorini G *et al.* (2009) *J Neurochem* **110**: 1538–1546. [PMID:19627441]
343. Gasnier B. (2000) *Biochimie* **82**: 327–337. [PMID:10865121]
344. Gasnier B. (2004) *Pflugers Arch* **447**: 756–759. [PMID:12750892]
345. Juge N *et al.* (2009) *J Biol Chem* **284**: 35073–35078. [PMID:19843525]
346. Martens H *et al.* (2008) *J Neurosci* **28**: 13125–13131. [PMID:19052203]
347. McIntire SL *et al.* (1997) *Nature* **389**: 870–876. [PMID:9349821]
348. Saito K *et al.* (2010) *Mol Brain* **3**: 40. [PMID:21190592]
349. Schiöth HB *et al.* (2013) *Mol Aspects Med* **34**: 571–585. [PMID:23506890]
350. Wojcik SM *et al.* (2006) *Neuron* **50**: 575–587. [PMID:16701208]
351. Zander JF *et al.* (2010) *J Neurosci* **30**: 7634–7645. [PMID:20519538]
352. Jonas MC *et al.* (2010) *J Cell Sci* **123** (Pt 19): 3378–3388. [PMID:20826464]
353. Kanamori A *et al.* (1997) *Proc Natl Acad Sci USA* **94**: 2897–2902. [PMID:9096318]
354. Lin P *et al.* (2008) *Am J Hum Genet* **83**: 752–759. [PMID:19061983]
355. Schlipf NA *et al.* (2010) *Eur J Hum Genet* **18**: 1065–1067. [PMID:20461110]
356. Andrini O *et al.* (2008) *Channels (Austin)* **2**: 346–357. [PMID:18989094]
357. Forster IC *et al.* (1999) *Am J Physiol* **276** (4 Pt 2): F644–F649. [PMID:10198426]
358. Ashikov A *et al.* (2005) *J Biol Chem* **280**: 27230–27235. [PMID:15911612]
359. Ishida N *et al.* (1998) *J Biochem* **124**: 171–178. [PMID:9644260]
360. Ishida N *et al.* (2005) *Genomics* **85**: 106–116. [PMID:15607426]
361. Ishida N *et al.* (1996) *J Biochem* **120**: 1074–1078. [PMID:9010752]
362. Ishida N *et al.* (1999) *J Biochem* **126**: 68–77. [PMID:10393322]
363. Kamiyama S *et al.* (2006) *J Biol Chem* **281**: 10945–10953. [PMID:16492677]
364. Kamiyama S *et al.* (2003) *J Biol Chem* **278**: 25958–25963. [PMID:12716889]
365. Lühn K *et al.* (2001) *Nat Genet* **28**: 69–72. [PMID:11326279]
366. Miura N *et al.* (1996) *J Biochem* **120**: 236–241. [PMID:8889805]
367. Muraoka M *et al.* (2001) *FEBS Lett* **495**: 87–93. [PMID:11322953]
368. Abbot EL *et al.* (2006) *Br J Pharmacol* **147**: 298–306. [PMID:16331283]
369. Agulhon C *et al.* (2003) *J Comp Neurol* **462**: 71–89. [PMID:12761825]
370. Boll M *et al.* (2002) *J Biol Chem* **277**: 22966–22973. [PMID:11959859]
371. Bröer S. (2008) *Physiology (Bethesda)* **23**: 95–103. [PMID:18400692]
372. Bröer S *et al.* (2008) *J Clin Invest* **118**: 3881–3892. [PMID:19033659]
373. Chen Z *et al.* (2003) *J Physiol (Lond)* **546** (Pt 2): 349–361. [PMID:12527723]
374. Chen Z *et al.* (2003) *Biochem Biophys Res Commun* **304**: 747–754. [PMID:12727219]
375. Edwards N *et al.* (2011) *Biochim Biophys Acta* **1808**: 260–270. [PMID:20691150]
376. Foltz M *et al.* (2005) *Biochem J* **386** (Pt 3): 607–616. [PMID:15504109]
377. Kennedy DJ *et al.* (2005) *Br J Pharmacol* **144**: 28–41. [PMID:15644866]
378. Larsen M *et al.* (2009) *Br J Pharmacol* **157**: 1380–1389. [PMID:19594759]
379. Larsen MH *et al.* (2008) *Eur J Pharmacol* **578**: 114–122. [PMID:17950272]
380. Metzner L *et al.* (2005) *FASEB J* **19**: 1468–1473. [PMID:16126914]
381. Pillai SM, Meredith D. (2011) *J Biol Chem* **286**: 2455–2460. [PMID:21097500]
382. Sagné C *et al.* (2001) *Proc Natl Acad Sci USA* **98**: 7206–7211. [PMID:11390972]
383. Thwaites DT, Anderson CM. (2011) *Br J Pharmacol* **164**: 1802–1816. [PMID:21501141]
384. Almqvist J *et al.* (2004) *Biochemistry* **43**: 9289–9297. [PMID:15260472]
385. Chen SY *et al.* (2008) *FASEB J* **22**: 2206–2213. [PMID:18337460]

386. Pan CJ *et al.* (2011) *PLoS ONE* **6**: e23157. [PMID:21949678]
387. Albers A *et al.* (2001) *Pflugers Arch* **443**: 92–101. [PMID:11692272]
388. Bröer A *et al.* (2002) *J Physiol (Lond)* **539** (Pt 1): 3–14. [PMID:11850497]
389. Fei YJ *et al.* (2000) *J Biol Chem* **275**: 23707–23717. [PMID:10823827]
390. Hatanaka T *et al.* (2001) *Biochim Biophys Acta* **1510**: 10–17. [PMID:11342143]
391. Hatanaka T *et al.* (2000) *Biochim Biophys Acta* **1467**: 1–6. [PMID:10930503]
392. Hägglund MG *et al.* (2011) *J Biol Chem* **286**: 20500–20511. [PMID:21511949]
393. Nakanishi T *et al.* (2001) *Biochem Biophys Res Commun* **281**: 1343–1348. [PMID:11243884]
394. Schiöth HB *et al.* (2013) *Mol Aspects Med* **34**: 571–585. [PMID:23506890]
395. Dalton TP *et al.* (2005) *Proc Natl Acad Sci USA* **102**: 3401–3406. [PMID:15722412]
396. Girijashanker K *et al.* (2008) *Mol Pharmacol* **73**: 1413–1423. [PMID:18270315]
397. Liu Z *et al.* (2008) *Biochem Biophys Res Commun* **365**: 814–820. [PMID:18037372]
398. Liuzzi JP *et al.* (2006) *Proc Natl Acad Sci USA* **103**: 13612–13617. [PMID:16950869]
399. Aguirre P *et al.* (2005) *BMC Neurosci* **6**: 3. [PMID:15667655]
400. De Domenico I *et al.* (2007) *Blood* **109**: 2205–2209. [PMID:17077321]
401. De Domenico I *et al.* (2005) *Proc Natl Acad Sci USA* **102**: 8955–8960. [PMID:15956209]
402. Donovan A *et al.* (2005) *Cell Metab* **1**: 191–200. [PMID:16054062]
403. Rice AE *et al.* (2009) *J Mol Biol* **386**: 717–732. [PMID:19150361]
404. Goytain A, Quamme GA. (2005) *Physiol Genomics* **21**: 337–342. [PMID:15713785]
405. Goytain A, Quamme GA. (2005) *Biochem Biophys Res Commun* **330**: 701–705. [PMID:15809054]
406. Kolisek M *et al.* (2012) *Am J Physiol, Cell Physiol* **302**: C318–C326. [PMID:22031603]
407. Sahni J, Scharenberg AM. (2013) *Mol Aspects Med* **34**: 620–628. [PMID:23506895]
408. Endeward V *et al.* (2008) *FASEB J* **22**: 64–73. [PMID:17712059]
409. Ripoche P *et al.* (2004) *Proc Natl Acad Sci USA* **101**: 17222–17227. [PMID:15572441]
410. Westhoff CM *et al.* (2002) *J Biol Chem* **277**: 12499–12502. [PMID:11861637]
411. Zidi-Yahiaoui N *et al.* (2009) *Am J Physiol, Cell Physiol* **297**: C537–C547. [PMID:19553567]
412. Babu E *et al.* (2003) *J Biol Chem* **278**: 43838–43845. [PMID:12930836]
413. Bodoy S *et al.* (2005) *J Biol Chem* **280**: 12002–12011. [PMID:15659399]
414. Wallgard E *et al.* (2008) *Arterioscler Thromb Vasc Biol* **28**: 1469–1476. [PMID:18483404]
415. Greinacher A *et al.* (2010) *Nat Med* **16**: 45–48. [PMID:20037594]
416. Inazu M *et al.* (2005) *J Neurochem* **94**: 1427–1437. [PMID:16000150]
417. Kommareddi PK *et al.* (2010) *Protein J* **29**: 417–426. [PMID:20665236]
418. Kouji H *et al.* (2009) *Arch Biochem Biophys* **483**: 90–98. [PMID:19135976]
419. Michel V, Bakovic M. (2009) *FASEB J* **23**: 2749–2758. [PMID:19357133]
420. Michel V *et al.* (2006) *Exp Biol Med (Maywood)* **231**: 490–504. [PMID:16636297]
421. Nair TS *et al.* (2004) *J Neurosci* **24**: 1772–1779. [PMID:14973250]
422. Nakamura T *et al.* (2010) *Biol Pharm Bull* **33**: 691–696. [PMID:20410607]
423. Traiffort E *et al.* (2005) *J Neurochem* **92**: 1116–1125. [PMID:15715662]
424. Uchida Y *et al.* (2009) *J Pharmacol Sci* **109**: 102–109. [PMID:19122366]
425. Wille S *et al.* (2001) *J Immunol* **167**: 5795–5804. [PMID:11698453]
426. Yabuki M *et al.* (2009) *Arch Biochem Biophys* **485**: 88–96. [PMID:19236841]
427. Yamada T *et al.* (2011) *Neurochem Int* **58**: 354–365. [PMID:21185344]
428. Graf J *et al.* (2005) *Hum Mutat* **25**: 278–284. [PMID:15714523]
429. Newton JM *et al.* (2001) *Am J Hum Genet* **69**: 981–988. [PMID:11574907]
430. Shimokawa N *et al.* (2002) *J Neurosci* **22**: 9160–9165. [PMID:12417639]
431. Nakai Y *et al.* (2007) *J Pharmacol Exp Ther* **322**: 469–476. [PMID:17475902]
432. Qiu A *et al.* (2006) *Cell* **127**: 917–928. [PMID:17129779]
433. Salojin KV *et al.* (2011) *Blood* **117**: 4895–4904. [PMID:21346251]
434. Chen Y *et al.* (2007) *J Pharmacol Exp Ther* **322**: 695–700. [PMID:17495125]
435. Ito S *et al.* (2010) *J Pharmacol Exp Ther* **333**: 341–350. [PMID:20065018]
436. Masuda S *et al.* (2006) *J Am Soc Nephrol* **17**: 2127–2135. [PMID:16807400]
437. Ohta KY *et al.* (2006) *Drug Metab Dispos* **34**: 1868–1874. [PMID:16928787]
438. Otsuka M *et al.* (2005) *Proc Natl Acad Sci USA* **102**: 17923–17928. [PMID:16330770]
439. Tanihara Y *et al.* (2007) *Biochem Pharmacol* **74**: 359–371. [PMID:17509534]
440. Terada T *et al.* (2006) *Pharm Res* **23**: 1696–1701. [PMID:16850272]
441. Tsuda M *et al.* (2009) *J Pharmacol Exp Ther* **329**: 185–191. [PMID:19164462]
442. Yasujima T *et al.* (2010) *Drug Metab Dispos* **38**: 715–721. [PMID:20047987]
443. Zhang X, Wright SH. (2009) *Am J Physiol Renal Physiol* **297**: F263–F271. [PMID:19515813]
444. O'Callaghan KM *et al.* (2010) *J Biol Chem* **285**: 381–391. [PMID:19875448]
445. Rajagopal A *et al.* (2008) *Nature* **453**: 1127–1131. [PMID:18418376]
446. White C *et al.* (2013) *Cell Metab* **17**: 261–270. [PMID:23395172]
447. Bodmer D *et al.* (2002) *Hum Mol Genet* **11**: 641–649. [PMID:11912179]
448. Chiabrando D *et al.* (2012) *J Clin Invest* **122**: 4569–4579. [PMID:23187127]
449. Duffy SP *et al.* (2010) *Mol Cell Biol* **30**: 5318–5324. [PMID:20823265]
450. Lipovich L *et al.* (2002) *Gene* **286**: 203–213. [PMID:11943475]
451. Meyer E *et al.* (2010) *Am J Hum Genet* **86**: 471–478. [PMID:20206334]
452. Quigley JG *et al.* (2004) *Cell* **118**: 757–766. [PMID:15369674]
453. Rajadhyaksha AM *et al.* (2010) *Am J Hum Genet* **87**: 643–654. [PMID:21070897]
454. Rey MA *et al.* (2008) *Haematologica* **93**: 1617–1626. [PMID:18815190]
455. Tailor CS *et al.* (1999) *J Virol* **73**: 6500–6505. [PMID:10400745]
456. Chen LQ *et al.* (2010) *Nature* **468**: 527–532. [PMID:21107422]
457. Tagoh H *et al.* (1996) *Biochem Biophys Res Commun* **221**: 744–749. [PMID:8630032]
458. Ballatori N *et al.* (2005) *Hepatology* **42**: 1270–1279. [PMID:16317684]
459. Christian WV *et al.* (2012) *J Biol Chem* **287**: 21233–21243. [PMID:22535958]
460. Dawson PA *et al.* (2005) *J Biol Chem* **280**: 6960–6968. [PMID:15563450]
461. Fang F *et al.* (2010) *J Neurochem* **115**: 220–233. [PMID:20649839]
462. Li N *et al.* (2007) *Biochem J* **407**: 363–372. [PMID:17650074]
463. Yao Y *et al.* (2010) *J Nutr* **140**: 1220–1226. [PMID:20463145]