Choline

Overview: The high-affinity, hemicholinium-3-sensitive, choline transporter (CHT, provisional nomenclature) is a member of the solute carrier family 5 (SLC5) of sodium-dependent transporters that, in mammals, includes the Na^+/substrate cotransporters for glucose, *myo*-inositol and iodide (Ferguson & Blakely, 2004; Wright & Turk, 2004). CHT contains 13 putative TM domains with an extracellular N-terminus and cytoplasmic C-terminus (Apparsundaram *et al*., 2000). CHT is expressed mainly in cholinergic neurones (kertatinocytes being an additional location) and through recapture of choline generated by the hydrolysis of ACh by acetylcholinesterase serves to maintain ACh synthesis within the presynaptic terminal (Ferguson & Blakely, 2004). Homozygous mice engineered to lack CHT die within 1 h of birth as a result of hypoxia arising from failure of transmission at the neuromuscular junction of the skeletal muscles that support respiration (Ferguson *et al*., 2004). 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 with weak Na^+ dependence have been described (Traiffort *et al*., 2005).

Nomenclature	**CHT**
Other names	CHT1, SLC5A7
Ensembl ID	ENSG00000115665
Endogenous substrates	Choline
Selective inhibitors	HC-3 (1–5 nM)
Probes	[^{3}H]-HC-3 (4–6 nM)
Stoichiometry	2–3 Na^+: 2–3 Cl^-: 1 choline

K_i and K_d values for hemicholinium-3 listed in the table are for human CHT expressed in *Xenopus laevis* oocytes (Okuda & Haga, 2000), or COS-7 cells (Apparsundaram *et al*., 2000). Hemicholinium mustard is a substrate for CHT that causes covalent modification and irreversible inactivation of the transporter.

Abbreviations: **HC-3**, hemicholinium-3

Further Reading:

BAZALAKOVA, M.H. & BLAKELY, R.D. (2006). The high-affinity choline transporter: a critical protein for sustaining cholinergic signaling as revealed in studies of genetically altered mice. *Handb. Exp. Pharmacol.,* **175,** 525–544.

FERGUSON, S.M. & BLAKELY, R.O. (2004). The choline transporter resurfaces: new roles for synaptic vesicles. *Mol. Interv.,* **4,** 22–37.

OKUDA, T. & HAGA, T. (2003). High-affinity choline transporter. *Neurochem. Res.,* **28,** 483–488.

SARTER, M. & PARIKH, V (2005). Choline transporters, cholinergic transmission and cognition. *Nat. Rev. Neurosci.,* **6,** 48–56.

WRIGHT, E.M. & TURK, E. (2004). The sodium/glucose cotransport family SLC5. *Pflûgers Arch.,* **447,** 510–518.

References:

APPARSUNDARAM, S. *et al*. (2000). *Biochem. Biophys. Res. Commun.,* **276,** 862–867.

FERGUSON, S.M. *et al*. (2004). *Proc. Natl. Acad, Sci. U.S.A.,* **101,** 8762–8767.

OKUDA, T. & HAGA, T. (2000). *FEBS Lett.,* **484,** 92–97.

TRAIFFORT, E. *et al*. (2005). *J. Neurochem.,* **92,** 1116–1125.

ALEXANDER, S.P.H., MATHIE, A. & PETERS, J.A. (2007). Guide to Receptors and Channels (GRAC), 2nd edition (2007 revision). *Br. J. Pharmacol.,* **150** (Suppl. 1), S1–S168.

GABA

Overview: Plasma membrane-located GABA transporters (provisional nomenclature as adopted for human GABA transporters) are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter receptor transporters that includes the monoamine and glycine transporters (Chen *et al*., 2003). The members of this superfamily share a structural motif of 12 TM segments (Palacín *et al*., 1998) that has been confirmed by the recent crystal structure of a bacterial homolog of the Na^+/Cl^--dependent neurotransmitter transporters from *Aquiflex aeolicus* (Yamashita *et al*., 2005). The activity of GABA-transporters located upon both neurones and glia serves to terminate GABA-ergic transmission, maintain low ambient extracellular concentrations of GABA, and recycle GABA for reuse by neurones. A structurally and functionally distinct vesicular transporter representing the SCL32 family (VGAT/VIAAT (ENSG00000101438); McIntire *et al*., 1997; Sagne *et al*., 1997; Gasnier, 2003), subject to inhibition by vigabatrin, is responsible for concentrating GABA (and glycine) within synaptic vesicles.

Nomenclature	**GAT-1**	**GAT-2**	**GAT-3**	**BGT-1**
Other names	mGAT-1, SLCA1	mGAT-3, SLCA16	mGAT-4, GAT-B, SLCA11	mGAT-2, SLCA12
Ensembl ID	ENSG00000157103	ENSG00000010379	ENSG00000132164	ENSG00000111181
Endogenous substrates	GABA	GABA, β-alanine	GABA, β-alanine	GABA, betaine
Selective inhibitors (IC_{50})	NNC-711 (0.04 μM), SKF89976A (0.13 μM), CI-966 (0.26 μM), tiagabine (0.8 μM), EF1500 (2 μM) (*R*)-EF1502 (4 μM), LU32-176B (4 μM) (*S*)-EF1502 (120 μM)	—	SNAP-5114 (6.6 μM)	NNC052090 (1.4 μM), (*R*)-EF1502 (22 μM), (*S*)-EF1502 (34 μM), (130 μM), LU 32176B (>100 μM)
Probes	[^{3}H]-tiagabine	—	—	—
Stoichiometry	$2Na^+$: $1Cl^-$: 1GABA	—	$\geq 2Na^+$: $2\ Cl^-$: 1GABA	$3Na^+$: 1 (or 2) Cl^-: 1GABA

SNAP-5114 is only weakly selective for GAT-3, with IC_{50} values in the range 20 to >30 μM at GAT-1, GAT-2 and BGT-1, whereas NNC052090 has at least an order of magnitude selectivity for BGT-1 (see Schousboe *et al*. (2004b) for a review). In addition to the inhibitors listed, EGYT3886 is a moderately potent, though nonselective, inhibitor of all cloned GABA transporters ($IC_{50} = 26-46$ μM; Dhar *et al*., 1994). 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 (Knutsen *et al*., 1999). 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 Schousboe *et al*. (2004a) for a review).

Abbreviations: **CI966**, [1-[2-[bis-4(trifluromethyl)phenyl]methoxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid; **EF1500**, *N*-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[*d*]isoxazol-3-ol; **EF1502**, *N*-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-(methylamino)4,5,6,7-tetrabenzo[*d*]isoxazol-3-ol; **EGYT3886**, (−)-2-phenyl-2-[(dimethylamino)ethoxy]-(1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptane; ***exo*-THPO**, 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-benzisoxazol; **LU32-176B**, *N*-[4,4-bis(4-fluorophenyl)-butyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; **NNC711**, 1-2-(((diphenylmethylene) amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride; **NNC052090**, 1-(3-(9*H*-carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol; **SKF89976A**, 1-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid

Further Reading:

CHEN, N.-H., REITH, M.E.A. & QUICK, M.W. (2004). Synaptic uptake and beyond: the sodium and chloride dependent neurotransmitter transporter family SLC6. *Pflügers Arch.,* **447,** 519–531.

CLARK, J.E. & CLARK, W.A. (2000). Pharmacology of GABA transporters. In: *Handbook of Experimental Pharmacology, Pharmacology of GABA and Glycine Neurotransmission,* ed. Möhler, H. Vol. 150. pp. 355–372. Berlin: Springer-Verlag.

DALBY, N.O. (2003). Inhibition of gamma-aminobutyric acid uptake: anatomy, physiology and effects against epileptic seizures. *Eur. J. Pharmacol.,* **479,** 127–137.

GADIA, A. & LOPEZ-COLOME, A.M. (2001). Glial transporters for glutamate, glycine and GABA: II. GABA transporters. *J. Neurosci. Res.,* **63,** 461–468.

GASNIER, B. (2004). The SLC32 transporter, a key protein for the synaptic release of inhibitory amino acids. *Pflügers Arch.,* **447,** 756–759.

HOG, S., GREENWOOD, J.R., MADSEN, K.B., LARSSON, O.M., FROLUND, B., SCHOUSBOE, A., KROGSGAARD-LARSEN, P. & CLAUSEN, R.P. (2006). Structure-activity relationships of selective GABA update inhibitors. *Curr. Top. Med. Chem.,* **6,** 1861–1882.

KANNER, B.I. (2000). Structure and function of GABA transporters. In: *Handbook of Experimental Pharmacology, Pharmacology of GABA and Glycine Neurotransmission*, ed. Möhler, H. Vol. 150. pp. 345–354. Berlin: Springer-Verlag.

PALACÍN, M., ESTÉVEZ, R., BERTRAN, J. & ZORANO, A. (1998). Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol. Rev.,* **78,** 969–1054.

RICHERSON, G.B. & WU, Y. (2004). Role of the GABA transporter in epilepsy. *Adv. Exp. Med. Biol.,* **548,** 76–91.

SARUP, A., LARSSON, O.M. & SCHOUSBOE, A. (2003). GABA Transporters and GABA-Transaminase as Drug Targets. *Curr. Drug Target CNS Neurol. Disord.,* **2,** 269–277.

SCHOUSBOE, A., SARUP, A., BAK, L.K., WAAGEPETERSEN, H.S. & LARSSON, O.M. (2004a). Role of astrocytic transport processes in glutamatergic and GABAergic neurotransmission. *Neurochem. Int.,* **45,** 521–527.

SCHOUSBOE, A., SARUP, A., LARSSON, O.M. & WHITE, H.S. (2004b). GABA transporters as drug targets for modulation of GABAergic activity. *Biochem. Pharmacol.,* **68,** 1557–1563.

SOUDIJN, W. & VAN WIJNGAARDEN, I. (2000). The GABA transporter and its inhibitors. *Curr. Med. Chem.,* **7,** 1063–1079.

References:

DHAR, T.G.M. *et al*. (1994). *J. Med. Chem.,* **37,** 2334–2342.

KNUTSEN, L.J.S. *et al*. (1999). *J. Med. Chem.,* **42,** 3447–3462.

MCINTIRE, S.L. *et al*. (1997). *Nature,* **389,** 870–876.

SAGNE, C. *et al*. (1997). *FEBS Lett.,* **417,** 177–183.

YAMASHITA, A. *et al*. (2005). *Nature,* **437,** 215–223.

ALEXANDER, S.P.H., MATHIE, A. & PETERS, J.A. (2007). Guide to Receptors and Channels (GRAC), 2nd edition (2007 revision). *Br. J. Pharmacol.,* **150** (Suppl. 1), S1–S168.

Glutamate (excitatory amino acid)

Overview: Plasma membrane located glutamate transporters (nomenclature proposed by Amara & Arriza, 1993) are members of the solute carrier family 1 (SLC1) of sodium-dependent transporters that also includes the neutral amino-acid transporters ASCT1 and ASCT2 (Palacín *et al*., 1998; Kanai & Hediger, 2003). Glutamate transporters present the unusual structural motif of eight TM segments and two re-entrant loops (Grunwald & Kanner, 2000). The crystal structure of a glutamate transporter homologue from *Pyrococcus horikosii* supports this topology and indicates that the transporter assembles as a trimer, where each monomer is a functional unit capable of substrate permeation (Yernool *et al*., 2004), in agreement with the proposed quaternary structure for EAAT2 (Gendreau *et al*., 2004). The activity of glutamate transporters located upon both neurones (predominantly EAAT3) and glia (predominantly EAAT1 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. Enhanced expression of EAAT2 resulting from administration of β-lactam antibiotics is neuroprotective (Rothstein *et al*., 2005). In addition, a thermodynamically uncoupled Cl^- flux, activated by Na^+ and glutamate (Kanner & Borre, 2002; Kanai & Hediger, 2003), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability. The transport and ion channel (Cl^- flux) function EAATs can be independently disrupted by site-directed mutagenesis, and for EAAT1 they have been shown to depend upon distinct functional domains (Ryan & Vandenberg, 2005). In the kidney, EAAT3 located in the apical membrane of proximal tubular cells is responsible for the reabsorption of glutamate (Hediger, 1999). Three structurally and functionally distinct vesicular glutamate transporters (VGLUT1, VGLUT2 and VGLUT3) of the SLC17 family are responsible for concentrating glutamate within synaptic vesicles (Reimer & Edwards, 2003).

Nomenclature	**EAAT1**	**EAAT2**	**EAAT3**
Other names	GLAST, SLC1A3	GLT1, SLC1A*2*	EAAC1, SLC1A1
Ensembl ID	ENSG000000079215	ENSG00000110436	ENSG00000106688
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate	L-glutamate, L-aspartate
Inhibitors (K_B or K_i)	DL-TBOA (9 μM)	DL-TBOA (0.12 μM), (2*S*,4*R*)-4-methylglutamate (3.4 μM), dihydrokainate (9 μM), *threo*-3-methylglutamate (18 μM)	DL-T-BOA (IC_{50} = 8 μM)
Probes	[^{3}H]-ETB-TBOA (K_D = 15.5 nM) [^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 16.2 nM), [^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 320 nM), [^{3}H]-D-aspartate, [^{3}H]-L-aspartate
Stoichiometry	—	$3Na^+ : 1H^+$: 1glutamate (in) : $1K^+$ (out)	$3Na^+ : 1H^+$: 1glutamate (in) : $1K^+$ (out)

Nomenclature	**EAAT4**	**EAAT5**
Other names	SLC1A6	SLC1A7
Ensembl ID	ENSG00000105143	ENSG00000162383
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate
Inhibitors (K_B or K_i)	DL-TBOA (4.4 μM), *Threo*-3-methylglutamate (50 μM)	DL-TBOA (3.2 μM)
Probes	[^{3}H]-ETB-TBOA (K_D = 24.8 nM), [^{3}H]-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-ETB-TBOA (K_D = 29.5 nM), [^{3}H]-D-aspartate, [^{3}H]-L-aspartate

The K_B (or K_i) values reported are derived from transporter currents mediated by EAATs expressed in voltage-clamped *Xenopus laevis* oocytes (Vandenberg *et al*., 1997; Shimamoto *et al*., 1998; Eliasof *et al*., 2001; Shigeri *et al*., 2001). K_B (or K_i) values derived in uptake assays are generally higher (e.g. Shimamoto *et al*., 1998). In addition to acting as a nontransportable inhibitor of EAAT2, (2*S*,4*R*)-4-methylglutamate, also known as SYM2081, is a competitive substrate for EAAT1 (K_M = 54 μM; Vandenberg *et al*., 1997) and additionally is a potent kainate receptor agonist (Zhou *et al*., 1997). Similarly, at concentrations that inhibit EAAT2, dihydrokainate binds to kainate receptors (Shimamoto *et al*., 1998). WAY-855 is a nontransportable inhibitor with selectivity for EAAT1, *versus* EAAT2, or EAAT3 (Dunlop *et al*., 2003), whereas WAY-213613 is a competitive inhibitor with selectivity for EAAT2 *versus* EAAT1, or EAAT3 (Dunlop *et al*., 2005). L-β-*threo*-benzyl-aspartate is a competitive non-substrate inhibitor that preferentially blocks EAAT3 *versus* EAAT1 or EAAT2 (Esslinger *et al*., 2005). [^{3}H]-[(2*S*,4*R*)-4-methylglutamate demonstrates high-affinity binding ($K_D \cong 6.0$ μM) to EAAT1 and EAAT2 in rat brain homogenates (Apricó *et al*., 2001) and EAAT1 in murine astrocyte membranes (Apricó *et al*., 2004), whereas [^{3}H]-ETB-TBOA binds with high affinity to all EAATs other than EAAT3 (Shimamoto *et al*., 2007). *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 (Eliasof *et al*., 2001). In addition to the agents listed in the table, DL-threo-β-hydroxyaspartate and L-*trans*-2,4-pyrolidine dicarboxylate act as nonselective 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 Vandenberg *et al*., 2004).

Abbreviations: **DL-TBOA**, DL-*threo*-β-benzyloxyaspartate; **ETO-TBOA**, (2*S*,3*S*)-3-{3-[4-ethylbenzoylamino]benzyloxy}aspartate; **WAY-855**, 3-amino-tricyclo[2.2.1.$0^{2,6}$]heptane-1,3-dicarboxylic acid; **WAY-213613**, *N*(4)-[4-(2-bromo-4,5-difluorophenoxy)phenyl]-L-asparagine

Further Reading:

AMARA, S.G. & FONTANA, A.C. (2002). Excitatory amino acid transporters: keeping up with glutamate. *Neurochem. Int.,* **41,** 313–318.

BEART, P.M. & O'SHEA, R.D, (2006). Transporters for L-glutamate: an update on their molecular pharmacology and pathological involvement. *Br. J. Pharmacol.* [Epub ahead of print].

BRIDGES, R.J. & ESSLINGER, C.S. (2005). The excitatory amino acid transporters: pharmacological insights on substrate and inhibitor specificity of EAAT subtypes. *J. Pharmacol. Exp. Ther.,* **107,** 271–285.

DANBOLT, N.C. (2001). Glutamate uptake. *Prog. Neurobiol.,* **65,** 1–105.

DUNLOP, V. (2006). Glutamate based therapeutic approaches: targeting the glutamate transport system. *Curr. Opin. Pharmacol.,* **6**, 103–107.

HEDIGER, M.A. (1999). Glutamate transporters in kidney and brain. *Am. J. Physiol.,* **277,** F487–F492.

HINOI, E., TAKARADA, T., TSUCHIHASHI, Y & YONEDA, Y (2005). Glutamate transporters as drug targets. *Curr. Drug Targets CNS Neurol. Disord.,* **4,** 211–220.

HUANG, Y.H. & BERGLES, D.E. (2004). Glutamate transporters bring competition to the synapse. *Curr. Opin. Neurobiol.,* **14,** 346–352.

KANAI, Y. & HEDIGER, M.A. (2003). The glutamate and neutral amino acid transporter family: physiological and pharmacological implications. *Eur. J. Pharmacol.,* **479,** 237–247.

KANAI, Y. & HEDIGER, M.A. (2004). The glutamate/neutral amino acid transporter family SLC1: molecular, physiological and pharmacological aspects. *Pflügers Arch.,* **447,** 465–468.

KANNER, B.I. & BORRE, L. (2002). The dual-function glutamate transporters: structure and molecular characterisation of the substrate-binding sites. *Biochim. Biophys. Acta,* **1555,** 92–95.

MARAGAKIS, N.J. & ROTHSTEIN, J.D. (2004). Glutamate transporters: animal models to neurologic disease. *Neurobiol. Dis.,* **15,** 461–473.

PALACÍN, M., ESTÉVEZ, R., BERTRAN, J. & ZORANO, A. (1998). Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol. Rev.,* **78,** 969–1054.

REIMER, R.J. & EDWARDS, R.H. (2004). Organic anion transport is the primary function of the SLC17/type I phosphate transporter family. *Pflügers Arch.,* **447,** 629–635.

RYAN, R.M. & VANDENBERG, R.J. (2005). A channel in a transporter. *Clin. Exp. Pharmacol. Physiol.,* **32,** 1–6.

SEAL, R.P. & AMARA, S.G. (1999). Excitatory amino acid transporters: a family in flux. *Annu. Rev. Pharmacol. Toxicol.,* **39,** 431–456.

SHIGERI, Y., SEAL, R.P. & SHIMAMOTO, K. (2004). Molecular pharmacology of glutamate transporters, EAATs and VGLUTs. *Brain Res. Brain Res. Rev.,* **45,** 250–265.

SONDERS, M.S., QUICK, M. & JAVITCH, J.A. (2005). How did the neurotransmitter cross the bilayer? A closer look. *Curr. Opin. Neurobiol.,* **15,** 296–304.

VANDENBERG, R.J., JU, P., AUBREY, K.R., RYAN, R.M. & MITROVIC, A.D. (2004). Allosteric modulation of neurotransmitter transporters at excitatory synapses. *Eur. J. Pharm. Sci.,* **23,** 1–11.

References:

AMARA, S.G. & ARRIZA, J.L. (1993). *Curr. Opin. Neurobiol.,* **3,** 337–344.

APRICO, K. *et al*. (2001). *J. Neurochem.,* **77,** 1218–1225.

APRICO, K. *et al*. (2004). *J. Neurosci. Res.,* **75,** 751–759.

DUNLOP, J. *et al*. (2003). *Br. J. Pharmacol.,* **140,** 839–846.

DUNLOP, J. *et al*. (2005). *Mol. Pharmacol.,* **68,** 974–982.

ELIASOF, S. *et al*. (2001). *J. Neurochem.,* **77,** 550–557.

ESSLINGER, C.S. *et al*. (2005). *Neuropharmacology,* **49**, 850–861.

GENDREAU, S. *et al*. (2004). *J. Biol. Chem.,* **279,** 39505–39512.

GRUNWALD, M. & KANNER, B.I. (2000). *J. Biol. Chem.,* **275,** 9684–9698.

ROTHSTEIN, J.D. *et al*. (2005). *Nature,* **433,** 73–77.

SHIGERI, Y. *et al*. (2001). *J. Neurochem.,* **79,** 279–302.

SHIMAMOTO, K. *et al*. (1998). *Mol. Pharmacol.,* **53,** 195–2001.

SHIMAMOTO, K. *et al*. (2007). *Mol. Pharmacol*. **71,** 294–302.

VANDENBERG, R.J. *et al*. (1995). *Mol. Pharmacol.,* **51,** 809–815.

YERNOOL, D. *et al*. (2004). *Nature,* **431,** 811–818.

ZHOU, L.M. *et al*. (1997). *J. Pharmacol. Exp. Ther.,* **280,** 422–427.

ALEXANDER, S.P.H., MATHIE, A. & PETERS, J.A. (2007). Guide to Receptors and Channels (GRAC), 2nd edition (2007 revision). *Br. J. Pharmacol.,* **150** (Suppl. 1), S1–S168.

Glycine

Overview: Plasma membrane-located glycine transporters (provisional nomenclature) are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter receptor transporters that includes the monoamine and GABA transporters (Chen *et al*., 2004). The members of this superfamily share a structural motif of 12 putative TM segments (Palacin *et al*., 1998) that has been confirmed by the recent crystal structure of a bacterial homolog of the Na^+/Cl^- dependent neurotransmitter transporters from *Aquiflex aeolicus* (Yamashita *et al*., 2005). 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 GlyT-2 (a,b & c) have also been identified (see Supplisson and Roux, 2002; Gomeza *et al*, 2003; Eulenberg et al., 2005; Betz *et al.,* 2006 for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission (Bergeron *et al*., 1998; Gabernet *et al*., 2005), but also are important in early neonatal life, for regulating glycine concentrations at inhibitory glycinergic synapses (Gomeza *et al*., 2003a). In addition, GlyT1 has been postulated to act as an organic osmolyte transporter important for cell volume regulation in cleavage-stage embryos (Steeves *et al*., 2003). Homozygous mice engineered to lack GlyT1 exhibit severe respiratory and motor deficiencies owing to hyperactive glycinergic signalling and die within the first postnatal day (Gomeza *et al*., 2003a; Tsai *et al*., 2004). GlyT2 transporters localised on the axons and boutons of glycinergic neurons appear crucial for efficient transmitter loading of synaptic vesicles but may not be essential for the termination of inhibitory neurotransmission (Gomeza *et al*., 2003b). Mice in which GlyT2 has been deleted develop a severe hyperekplexia phenotype during the second postnatal week and subsequently die (Gomeza *et al*., 2003b). A structurally and functionally distinct vesicular transporter (VGAT/VIAAT (ENSG00000101438); McIntire *et al*., 1997; Sagne *et al*., 1997), subject to inhibition by vigabatrin, is responsible for concentrating glycine (and GABA) within synaptic vesicles.

Nomenclature	**GlyT1**	**GlyT2**
Other names	SLC6A9	SLC6A5
Ensembl ID	ENSG00000117413	ENSG00000165970
Endogenous substrates	Glycine	Glycine
Selective inhibitors (IC_{50})	(*R*)-NFPS (0.8–3 nM), NFPS (3 nM), SSR504734 (18 nM), NPTS (37 nM), Org 24598	ALX 1393, ALX 1405, Org 25543 (20 nM)
Probes (K_D)	[^{3}H]-(*R*)-NPTS (1 nM), [^{3}H]-NFPS (7–21 nM)	—
Stoichiometry	$2Na^+$: $1Cl^-$: 1 glycine	$3Na^+$: $1Cl^-$: 1 glycine

In addition to the inhibitors listed, sarcosine is a selective inhibitor of and substrate for GlyT1. Inhibition of GLYT1 by NFPS is non-competitive (Mallorga *et al*., 2003). IC_{50} values for Org 24598 reported in the literature vary, most likely due to differences in assay conditions (Brown, 2001; Mallorga *et al*., 2003). The tricyclic antidepressant amoxapine weakly inhibits GlyT2 (IC_{50} 92 μM) with approximately 10-fold selectivity over GlyT1 (Nunez *et al*., 2000). The endogenous lipids arachidonic acid and anandamide exert opposing effects upon GlyT1a, inhibiting ($IC_{50} \sim 2\,\mu$M) and potentiating ($EC_{50} \sim 13\,\mu$M) transport currents, respectively (Pearlman *et al*., 2003). N-arachidonyl-glycine has recently been described as a non-competitive inhibitor of GlyT2a, but not GlyT1b (Wiles *et al.,* 2006). Protons (Aubrey *et al*., 2000) and Zn^{2+} (Ju *et al*., 2004) act as non-competitive inhibitors of GlyT1b, with IC_{50} values of $\sim$100 nM and $\sim$10 μM, respectively, but neither ion affects GlyT2 (reviewed by Vandenberg *et al*., 2004).

Abbreviations: **ALX 1393**, O-[2-benzyloxyphenyl-3-flurophenyl]methyl-L-serine; **ALX 1405**, structure not available; **NFPS**, N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine, also known as ALX5407; **NPTS**, (*N*-[3-phenyl-3-(4′-(4-toluoyl) phenoxy)propyl]sarcosine; **Org 24598**, *R*-(−)-*N*-[3-[(4-triflouromethyl)phenoxy]-3-phenyl-propylglycine; **Org 25543**, 4-benzyloxy-3,5-dimethoxy-*N*-[1-(dimethylaminocyclopentyl) methyl] benzamide; **SSR504734**, 2-chloro-[*N*-(S)-phenyl[(2S)-piperdin-2-yl]methyl]-3-trifluoromethyl benzamide

Further Reading:

ARAGÓN, C. & LOPEZ-CÓRCUERA, B. (2003). Structure, function and regulation of glycine neurotransporters. *Eur. J. Pharmacol.,* **479,** 249–262.

ARAGÓN, C. & LOPEZ-CÓRCUERA, B. (2005). Glycine transporters: crucial roles of pharmacological interest revealed by gene deletion. *Trends Pharmacol Sci.,* **26,** 283–286.

BETZ, H., GOMEZA, J., SCHOLZE, P. & EULENBERG, V. (2006). Glycine transporters: essential regulators of synaptic transmission. *J. Neurochem*., **97**, 1600–1610.

BRASNJO, G. & OTIS, T.S. (2003). Glycine transporters not only take out the garbage, they recycle. *Neuron,* **40,** 667–669.

CHEN, N.-H., REITH, M.E.A. & QUICK, M.W. (2004). Synaptic uptake and beyond: the sodium and chloride dependent neurotransmitter transporter family SLC6. *Pflügers Archiv.,* **447,** 519–531.

EULENBURG, V., ARMSEN, W., BETZ, H. & GOMEZA, J. (2005). Glycine transporters: essential regulators of neurotransmission. *Trends Biochem. Sci.,* **30,** 325–333.

GADEA, A. & LOPEZ-COLOME, A.M. (2001). Glial transporters for glutamate, glycine, and GABA III. Glycine transporters. *J. Neurosci. Res.,* **64,** 218–222.

GOMEZA, J., OHNO, K. & BETZ, H. (2003). Glycine transporter isoforms in the mammalian central nervous system: structures, functions and therapeutic promises. *Curr. Opin. Drug Discov. Devel.,* **6,** 675–682.

LECHNER, S.M. (2006). Glutamate-based therapeutic approaches: inhibitors of glycine transport. *Curr. Opin. Pharmacol.,* **6**, 75–81.

PALACÍN, M., ESTÉVEZ, R., BERTRAN, J. & ZORANO, A. (1998). Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol. Rev.,* **78,** 969–1054.

SUPPLISSON, S. & ROUX, M.J. (2002). Why glycine transporters have different stoichiometries. *FEBS Lett.,* **529,** 93–101.

SUR, C. & KINNEY, G.G. (2004). The therapeutic potential of glycine transporter-1 inhibitors. *Expert. Opin. Investig. Drugs.,* **13,** 515–521.

VANDENBERG, R.J., JU, P., AUBREY, K.R., RYAN, R.M. & MITROVIC, A.D. (2004). Allosteric modulation of neurotransmitter transporters at excitatory synapses. *Eur. J. Pharm. Sci.,* **23,** 1–11.

References:

AUBREY, K.R. *et al*. (2000). *Mol. Pharmacol.,* **58,** 129–135.

BERGERON, R. *et al*. (1998). *Proc. Natl. Acad. Sci. USA,* **95,** 15730–15734.

BROWN, A. (2001). *Bioorg. Med. Chem. Lett.,* **11,** 2007–2009.

GABERNET, L. *et al*. (2005). *Neurosci. Lett.,* **373,** 79–84.

GOMEZA, J. *et al*. (2003a). *Neuron,* **40,** 785–796.

GOMEZA, J. *et al*. (2003b). *Neuron,* **40,** 797–806.

JU, P. *et al*. (2004). *J. Biol. Chem.,* **279,** 22983–22991.

MALLORGA, P.J. *et al*. (2003). *Neuropharmacology,* **45,** 585–593.

MCINTIRE, S.L. *et al*. (1997). *Nature,* **389,** 870–876.

NUNEZ, E. *et al*. (2000). *Br. J. Pharmacol.,* **129,** 200–206.

PEARLMAN, R.J. *et al*. (2003). *J. Neurochem.,* **84,** 592–601.

SAGNE, C. *et al*. (1997). *FEBS Lett.,* **417,** 177–183.

STEEVES, C.L. *et al*. (2003). *Proc. Natl. Acad. Sci. USA,* **100,** 13982–13987.

TSAI, G. *et al*. (2004). *Proc. Natl. Acad. Sci. USA,* **101,** 8485–8490.

WILES, A.L. *et al*. (2006). *J. Neurochem*., **99,** 781–786.

YAMASHITA, A. *et al*. (2005). *Nature,* **437,** 215–223.

ALEXANDER, S.P.H., MATHIE, A. & PETERS, J.A. (2007). Guide to Receptors and Channels (GRAC), 2nd edition (2007 revision). *Br. J. Pharmacol.,* **150** (Suppl. 1)**,** S1–S168.

Monoamine

Overview: Plasma membrane located monoamine transporters (provisional nomenclature) transport the hormone/transmitters adrenaline, noradrenaline, dopamine and 5-hydroxytryptamine, and are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter transporters that includes the GABA and glycine transporters (Chen *et al*., 2003). The members of this superfamily share a structural motif of 12 putative transmembrane segments (Palacín *et al*., 1998). A high resolution structure of a bacterial homologue of these transporters has been reported recently (Yamashita *et al*., 2005).

Nomenclature	**DAT**	**NET**	**SERT**
Other names	DAT1, SLC6A3	NAT1, SLC6A2	5-HTT, SERT1, SLC6A4
Ensembl ID	ENSG00000142319	ENSG00000103546	ENSG00000108576
Endogenous substrates	Dopamine, adrenaline, noradrenaline	Noradrenaline, adrenaline, dopamine	5-HT
Synthetic substrates	Amphetamine, methamphetamine, MPP^+	Amphetamine, methamphetamine, MPP^+	*p*-Chloroamphetamine, MDMA
Selective inhibitors	Mazindol (8.0), WIN35428 (7.9), GBR12935 (7.6)	Mazindol (8.9), nisoxetine (8.4), nomifensine (8.1)	Paroxetine (9.6, Tatsumi *et al*., 1997), sertraline (9.1), fluoxetine (8.5, Tatsumi *et al*., 1997)
Probes	[^{3}H]-GBR12935 (3 nM, Pristupa *et al*., 1994), [^{3}H]-WIN35428 (10 nM, Pristupa *et al*., 1994)	[^{3}H]-Mazindol (0.5 nM), [^{3}H]-nisoxetine (4 nM)	[^{3}H]-Paroxetine (0.2 nM), [^{3}H]-citalopram (5 nM)
Predicted stoichiometry	1 Dopamine:1–2 Na^+:1 Cl^- (Gu *et al*., 1994)	1 Noradrenaline: 1 Na^+:1 Cl^- (Gu *et al*., 1996)	1 5-HT:1 Na^+:1 Cl^- (in), +1 K^+ (out) (Talvenheimo *et al*., 1983)

[^{125}I]-RTI55 labels all three transporters 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.

Abbreviations: **GBR12935**, 1-(2-[diphenylmethoxy]ethyl)-4-(3-phenylpropyl)piperazine; **MDMA**, 3,4-methylenedioxymethamphetamine; **MPP^+**, 1-methyl-4-phenylpyridinium; **RTI55**, 2β-carbomethoxy-3β-(4-iodophenyl) tropane (also known as β-CIT); **WIN35428**, 2β-carboxymethy-3β-(4-fluorophenyl)tropane (also known as β-CFT).

Further Reading:

CHEN, N.-H., REITH, M.E.A. & QUICK, M.W. (2003). Synaptic uptake and beyond: the sodium and chloride dependent neurotransmitter transporter family SLC6. *Pflügers Archiv.,* **447,** 519–531.

LESTER, H.A. *et al*. (1996). Listening to neurotransmitter transporters. *Neuron,* **17,** 807–810.

MASSON, J., SAGNE, C., HAMON, M. & EL-MESTIKAWY, S. (1999). Neurotransmitter transporters in the central nervous system. *Pharmacol. Rev.,* **51,** 439–464.

OWENS, M.J., MORGAN, W.N., PLOTT, S.J. & NEMEROFF, C.B. (1997). Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J. Pharmacol. Exp. Ther.,* **283,** 1305–1322.

PALACÍN, M., ESTÉVEZ, R., BERTRAN, J. & ZORANO, A. (1998). Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol Rev.,* **78,** 969–1054.

RUDNICK, G. (2002). Mechanisms of biogenic amine neurotransmitter transporters. In: *Neurotransmitter Transporters: Structure, Function, and Regulation*, ed. Reith, M.E.A., 2nd edn, pp. 25–52. Totawa, NJ: Humana Press.

TORRES, G.E., GAINETDINOV, R.R. & CARON, M.G. (2003). Plasma membrane monoamine transporters: structure, regulation and function. *Nat. Rev. Neurosci.,* **4,** 13–25.

ZAHNISER, N.R. & DOOLEN, S. (2001). Chronic and acute regulation of Na^+/Cl^--dependent neurotransmitter transporters: drugs, substrates, presynaptic receptors, and signaling systems. *Pharmacol. Ther.,* **92,** 21–55.

References:

GU, H. *et al*. (1994). *J. Biol. Chem.,* **269,** 7124–7130.

GU, H.H. *et al*. (1996). *J. Biol. Chem.,* **271,** 6911–6916.

PRISTUPA, Z.B. *et al*. (1994). *Mol. Pharmacol.,* **45,** 125–135.

TALVENHEIMO, J. *et al*. (1983). *J. Biol. Chem.,* **258,** 6115–6119.

TATSUMI, M. *et al*. (1997). *Eur. J. Pharmacol.,* **340,** 249–258.

YAMASHITA, A. *et al*. (2005). *Nature,* **437,** 215–223.

ALEXANDER, S.P.H., MATHIE, A. & PETERS, J.A. (2007). Guide to Receptors and Channels (GRAC), 2nd edition (2007 revision). *Br. J. Pharmacol.,* **150** (Suppl. 1), S1–S168.

Nucleoside

Overview: Nucleoside transporters are divided into two families, the equilibrative, solute carrier family 29 (SLC29) and the sodium-dependent, solute carrier family 28 (SLC28), where the endogenous substrates are nucleosides. Structurally, SLC29 family members appear to be composed of 11 transmembrane segments, while the SLC28 family members have 13 transmembrane segments, both with cytoplasmic N-termini and extracellular C-termini.

Nomenclature	**ENT1**	**ENT2**
Other names	*es*, NBTI-sensitive, SLC29A1	*ei*, NBTI-insensitive, SLC29A2
Ensembl ID	ENSG00000112759	ENSG00000174669
Endogenous substrates	Adenosine, guanosine, inosine, uridine, thymidine, cytidine	Adenosine, guanosine, inosine, uridine, thymidine, hypoxanthine
Synthetic substrates	2-Chloroadenosine, dideoxyinosine, formycin B, tubercidin, vidarabine, cytarabine, AZT, cladribine, pentostatin, zalcitabine, didanosine, floxidine, gemcitabine	2-Chloroadenosine, formycin B, tubercidin, cytarabine, cladribine, vidarabine, gemcitabine
Selective inhibitors	NBTI (9.7), draflazine (9.5), KF24345 (9.4, Hammond & Archer, 2004), NBTGR (9.3), dilazep (9), dipyridamole (8.5)	—
Probes	[^{3}H]-NBTI (0.5 nM)	—
Predicted stoichiometry	Equilibrative	Equilibrative

The affinities of draflazine, dilazep, KF24345 and dipyridamole at ENT1 transporters are species dependent, exhibiting lower affinity at rat transporters than at human transporters (Sundaram *et al*., 1998; Hammond & Archer, 2004). Additional members of the family have been identified (including ENT3 [SLC29A3, ENSG00000156604] and ENT4 [SLC29A4, ENSG00000164638]), which have recently been reported to be intracellular purine nucleoside transporters (Baldwin *et al*., 2005).

Nomenclature	**CNT1**	**CNT2**	**CNT3**
Other names	N2/*cit*, SLC28A1	N1/*cif*, SPNT, SLC28A2	N3/*cib*, SLC28A3
Ensembl ID	ENSG00000156222	ENSG00000137860	ENSG00000099118
Endogenous substrates	Uridine, cytidine, thymidine, adenosine	Adenosine, guanosine, inosine, thymidine	Uridine, cytidine, thymidine, adenosine, guanosine, inosine
Synthetic substrates	AZT, zalcitabine, gemcitabine	Formycin B, cladribine, fludarabine, vidarabine, didanosine	AZT, zalcitabine, didanosine, formycin B, 5-fluorouridine, 5-fluoro-2′-deoxyuridine, zebularine, gemcitabine, cladribine, fludarabine
Predicted stoichiometry	1 : 1 Na^+	1 : 1 Na^+	1 : 2 Na^+

A further two Na^+-dependent (1 : 1 Na^+ stoichiometry) 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).

Abbreviations: **AZT**, 3′-azido-3′-deoxythymidine; **NBTI**, nitrobenzylthioinosine (also known as **NBMPR**); **NBTGR**, nitrobenzylthioguanosine; **KF24345**, 3-(1-[6,7-diethoxy-2-morpholinoquinazolin-4-yl]piperidin-4-yl)-1,6-dimethyl-2,4(1*H*,3*H*)-quinazolinedione hydrochloride

Further Reading:

ACIMOVIC, Y. & COE, I.R. (2002). Molecular evolution of the equilibrative nucleoside transporter family: identification of novel family members in prokaryotes and eukaryotes. *Mol. Biol. Evol.,* **19,** 2199–2210.

BALDWIN, S.A., BEAL, P.R., YAO, S.Y., KING, A.E., CASS, C.E. & YOUNG, J.D. (2004). The equilibrative nucleoside transporter family, SLC29. *Pflüger's Arch.,* **447,** 735–743.

CLARKE, M.L., MACKEY, J.R., BALDWIN, S.A., YOUNG, J.D. & CASS, C.E. (2002). The role of membrane transporters in cellular resistance to anticancer nucleoside drugs. *Cancer Treat. Res.,* **112,** 27–47.

GRAY, J.H., OWEN, R.P. & GIACOMINI, K.M. (2004). The concentrative nucleoside transporter family, SLC28. *Pflüger's Arch.,* **447,** 728–734.

HYDE, R.J., CASS, C.E., YOUNG, J.D. & BALDWIN, S.A. (2001). The ENT family of eukaryote nucleoside and nucleobase transporters: recent advances in the investigation of structure/function relationships and the identification of novel isoforms. *Mol. Membr. Biol.,* **18,** 53–63.

KING, A.E., ACKLEY, M.A., CASS, C.E., YOUNG, J.D. & BALDWIN, S.A. (2006). Nucleoside transporters: from scavengers to novel therapeutic targets. *Trends Pharmacol. Sci.,* **27,** 416–425.

References:

BALDWIN, S.A. *et al*. (2005). *J. Biol. Chem.,* **280,** 15880–15887.

HAMMOND, J.R. & ARCHER, R.G.E. (2004). *J. Pharmacol. Exp. Ther.,* **308,** 1083–1093.

SUNDARAM, M. *et al*. (1998). *J. Biol. Chem.,* **273,** 21519–21525.

ALEXANDER, S.P.H., MATHIE, A. & PETERS, J.A. (2007). Guide to Receptors and Channels (GRAC), 2nd edition (2007 revision). *Br. J. Pharmacol.,* **150** (Suppl. 1), S1–S168.