CELL SURFACE TRANSMITTER TRANSPORTERS

GABA

Overview: Plasma membrane located GABA transporters are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter transporters that includes the monoamine and glycine transporters (Chen *et al*., 2004). The members of this superfamily share a structural motif of 12 putative TM segments (Palacín *et al*., 1998). 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 and glia. A structurally and functionally distinct vesicular transporter representing the SLC32 family (VGAT/VIAAT (ENSG00000101438); McIntire *et al*., 1997; Sagne *et al*., 1997; Gasnier, 2004), subject to inhibition by vigabatrin, is responsible for concentrating GABA (and glycine) within synaptic vesicles. There is presently no recommendation from NC-IUPHAR concerning the nomenclature of GABA transporters. The nomenclature adopted here is that used for human GABA transporters.

Nomenclature	**GAT-1**	**GAT-2**	**GAT-3**	**BGT-1**
Other names	mGAT-1	mGAT3	mGAT4, GAT-B	mGAT2
Ensembl ID	ENSG00000157103	ENSG00000010379	ENSG00000132164	ENSG00000111181
Endogenous substrates	GABA	GABA, β-alanine	GABA, β-alanine	GABA, betaine
Selective inhibitors (IC_{50})	NNC711 (0.04 μM), tiagabine (0.08 μM), SKF89976A (0.13 μM), CI966 (0.26 μM), EF1502 (4 μM)	—	SNAP5114 (6.6 μM)	NNC052090 (1.4 μM), EF1502 (22 μM)
Radioligands	[^{3}H]-tiagabine	—	—	—
Stoichiometry	$2Na^+$: $1Cl^-$: 1GABA	—	—	$3Na^+$: 1 (or 2) Cl^-: 1GABA

SNAP5114 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 non-selective, 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; **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; **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

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Glutamate (excitatory amino acid)

Overview: Plasma membrane located glutamate transporters (nomenclature as proposed by Amara & Arriza, 1993) transport both L-glutamate and L-asparate, and 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 8TM segments and 1 (Seal *et al*., 2000), or 2 (Grunwald & Kanner, 2000), re-entrant loops. The recently determined crystal structure of a glutamate transporter orthologue from *Pyrococcus horikosii* supports the latter scheme 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, 4 & 5) and glia (predominantly EAAT 1 & 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 in the glutamate-glutamine cycle. In addition, a thermodynamically uncoupled Cl^- flux, activated by Na^+ and glutamate (Kanner & Borre, 2002; Kanai & Hediger, 2003; 2004), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability. 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, 2 & 3) of the SLC17 family are responsible for concentrating glutamate within synaptic vesicles (Reimer & Edwards, 2004).

Nomenclature	**EAAT1**	**EAAT2**	**EAAT3**
Other names	GLAST	GLT1	EAAC1
Ensembl ID	ENSG000000079215	ENSG00000110436	ENSG00000106688
Inhibitors	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-TBOA ($IC_{50} = 8$ μM)
Radioligands	[^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H-D-aspartate, [^{3}H]-L-aspartate	[^{3}H]-[(2*S*,4*R*)-4-methylglutamate, [^{3}H-D-aspartate, [^{3}H]-L-aspartate	[^{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	—	—
Ensembl ID	ENSG00000105143	ENSG00000162383
Endogenous substrates	L-glutamate, L-aspartate	L-glutamate, L-aspartate
Radioligands	[^{3}H-D-aspartate, [^{3}H]-L-aspartate	[^{3}H-D-aspartate, [^{3}H]-L-aspartate
Inhibitors	DL-TBOA (4.4 μM), *threo*-3-methylglutamate (50 μM)	DL-TBOA (3.2 μM)

The K_b (or K_i) values reported in the table 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 non-transportable 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 is also 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 has recently been described as a non-transportable inhibitor with selectivity for EAAT1, *versus* EAAT2, or EAAT3 (Dunlop *et al*., 2003). [^{3}H]-[(2*S*,4*R*)-4-methylglutamate demonstrates low 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). *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 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 Vandenberg *et al*., 2004).

Abbreviations: **DL-TBOA,** DL-*threo*-β-benzyloxyaspartate; **WAY-855**, 3-amino-tricyclo[2.2.1.0^{2,6}]heptane-1,3-dicarboxylic acid

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Glycine

Overview: Plasma membrane located glycine transporters (provisional nomenclature) are members of the solute carrier family 6 (SLC6) of sodium- and chloride-dependent neurotransmitter 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 (Palacín *et al*., 1998). 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, e & f) differing in their N- and C-termini are generated by alternative promoter usage and splicing, and two splice variants of GlyT-2 (a & b) have also been identified (see Supplisson & Roux, 2002; Gomeza *et al*., 2003 for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission (Bergeron *et al*., 1998), but also are important in early neonatal life, 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 due 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 neurones are likely to play a role in the termination of inhibitory neurotransmission and appear crucial for efficient transmitter loading of synaptic vesicles (Gomeza *et al*., 2003b). Mice in which GlyT2 has been deleted develop a severe hyperekplexia phenotype during the second postnatal week and subsequently and 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**
Ensembl ID	ENSG00000117413	ENSG00000165970
Endogenous substrates	Glycine	Glycine
Selective inhibitors (IC_{50})	(*R*)-NFPS (ALX 5407) (0.8–3 nM), NFPS (3 nM), NPTS(37 nM), Org 24598	ALX1393, ALX1405, Org25543 (20 nM)
Radioligands	[^{3}H]-(*R*)-NPTS(1 nM), [^{3}H]-NFPS (7–21 nM)	—
Stoichiometry	$2Na^+$: $1Cl^-$: 1 glycine	3 Na^+: $1Cl^-$: 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 *et al*., 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 ($IC_{50} \sim 2$ μM) and potentiating ($EC_{50} \sim 13$ μM) transport currents, respectively (Pearlman *et al*., 2003). Protons (Aubrey *et al*., 2000) and Zn^{2+} (Ju *et al*., 2004) 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 Vandenberg *et al*., 2004).

Abbreviations: **ALX1393**, *O*-[2-benzyloxyphenyl-3-flurophenyl]methyl-L-serine; **ALX1405**, structure not available; **NFPS**, *N*-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine; **NPTS**, (*N*-[3-phenyl-3-(4′-(4-toluoyl) phenoxy)propyl]sarcosine; **Org24598**, *R*-(-)-*N*-[3-[(4-triflouromethyl)phenoxy]-3-phenyl-propylglycine; **Org25543**, 4-benzyloxy-3,5-dimethoxy-*N*-[1-(dimethylaminocyclopentyl) methyl] benzamide.

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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*., 2004). The members of this superfamily share a structural motif of 12 putative transmembrane segments (Palacín *et al*., 1998).

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)
Radioligands	[^{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)

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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 TM segments, while the SLC28 family have 13 TM 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)	—
Radioligands	[^{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]) but are incompletely characterised (see Hyde *et al*., 2001; Acimovic & Coe, 2002; Baldwin *et al*., 2004).

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

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