Glycine transporters

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 (Palacín *et al*., 1998) that has been confirmed by the crystal structure of a bacterial homolog of the Na^+/Cl^--dependent neurotransmitter transporters from *Aquiflex aeolicus* ($LeuT_{Aa}$) (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 GlyT2 (a, b & c) have also been identified (see Supplisson and Roux, 2002; Eulenburg *et al*., 2005; Betz *et al*., 2006; Gomeza *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). 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 (Gomeza *et al*., 2003a; Tsai *et al*., 2004). 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 (Yee *et al*., 2006). GlyT2 transporters localized 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 (Gomeza *et al*., 2003b; Rousseau *et al*., 2008). Mice in which GlyT2 has been deleted develop a fatal hyperekplexia phenotype during the second postnatal week (Gomeza *et al*., 2003b) and mutations in the human gene encoding GlyT2 (*SLC6A5*) have been identified in patients with hyperekplexia (reviewed by Harvey *et al*., 2008). 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 (ALX 5407) (0.8–3 nM), SSR103800 (2 nM), *N*-methy-SSR504734 (2.5 nM), NFPS (3 nM), LY2365109 (16 nM), SSR504734 (18–314 nM), NPTS (37 nM), Org 24598	ALX 1393, ALX 1405, Org 25543 (20 nM)
Radioligands (K_D)	[^{3}H]-(*R*)-NPTS (1 nM), [^{35}S]ACPPB (2 nM), [^{3}H]-*N*-methyl-SSR504734 (3.3–8.1 nM), [^{3}H]-NFPS (7–21 nM),	–
Stoichiometry	2 Na^+ : 1 Cl^- : 1 glycine	3 Na^+ : 1 Cl^- : 1 glycine

In addition to the inhibitors listed, sarcosine is a selective transportable inhibitor of GlyT1, but has no affect on GlyT2. This difference has been attributed to a single glycine residue in transmembrane domain 6 (serine residue in GlyT2) (Vandenberg *et al*., 2007). Inhibition of GLYT1 by the sarcosine derivatives NFPS, NPTS and Org24598 is non-competitive (Mallorga *et al*., 2003; Mezler *et al*., 2008). 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} ~2 μM) and potentiating (EC_{50} ~13 μM) 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 ~100 nM and ~10 μM respectively, but neither ion affects GlyT2 (reviewed by Vandenberg *et al*., 2004).

Abbreviations: **ACPPB**, (S)-2-amino-4-chloro-*N*-(1-(4-phenyl-1-(propylsulfonyl)piperidin-4-yl)ethyl)benzamide; **ALX 1393**, O-[2-benzyloxyphenyl-3-flurophenyl]methyl-L-serine; **ALX 1405**, structure not available; **LY2365109**, {[2-(4-benzo[1,3]dioxol-5-yl-2-tert-butylphenoxy)ethyl]-methylamino}-acetic acid; **NFPS**, N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine; **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; **SSR103800**, structure not available; **SSR504734**, 2-chloro-[*N*-(*S*)-phenyl[(2*S*)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide

Further Reading

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