

Glycine Transporters

Key References

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Overview

Glycine is an important inhibitory neurotransmitter in the mammalian CNS where it acts via strychnine-sensitive glycine receptors. It can also produce excitatory effects via strychnine-insensitive glycine sites located on NMDA glutamate receptors. Extracellular glycine levels can be regulated via uptake by high affinity glycine transporters. Two distinct subtypes of glycine transporter, referred to as GlyT-1 and GlyT-2, have been characterized. Both are members of the sodium/chloride-dependent family of transporters, which also includes transporters for GABA and biogenic amines.

In terms of structure, GlyT-1 and GlyT-2 each possess 12 putative transmembrane spanning domains, and share approximately 50% amino acid sequence identity. GlyT-1 exists in multiple isoforms that differ only in their amino terminal sequences. Although these isoforms can vary in their distribution, expression and developmental regulation, there is no evidence that they differ in their functional properties or pharmacology. Two isoforms of GlyT-2 have also been reported.

GlyT-1 is widely expressed both in peripheral tissues and in the CNS where it is present predominantly on glial cells. GlyT-1 is likely to be the main high affinity transporter responsible for glycine uptake, and in some brain regions it appears to be co-localized with NMDA glutamate receptors. Originally it was thought that the glycine binding sites on these receptors were normally saturated with glycine, but studies now indicate that glycine transport can maintain local glycine concentrations at sub-saturating levels. This suggests that GlyT-1 could play a physiological role in regulating glutamatergic neurotransmission, a concept that is supported by recent gene knockout studies, in

which reduced GlyT-1 expression enhanced NMDA receptor function. Gene knockout studies also indicate that GlyT-1 is important in regulating glycine levels at inhibitory strychnine-sensitive glycine receptors.

In contrast to GlyT-1, GlyT-2 has a more limited distribution, being present mainly on inhibitory glycinergic neurons in the spinal cord, brainstem and cerebellum. Recent knockout studies suggest that a major physiological role of GlyT-2 is likely to be replenishment of glycine in presynaptic terminals. Thus, while it was thought previously that GlyT-1 and GlyT-2 played similar roles in regulating glycine levels in different regions of the brain, it now seems more likely that GlyT-1 is the main regulator of glycine levels throughout the CNS, while GlyT-2 has a more specialized role in maintaining terminal supplies of glycine for inhibitory glycinergic neurotransmission.

There are now a number of potent GlyT inhibitors that are selective for either GlyT-1 or GlyT-2 (see Table). Selective GlyT-1 inhibitors have been shown to increase extracellular glycine levels and potentiate NMDA receptor-mediated activity both *in vitro* and *in vivo*. GlyT-1 inhibitors have also displayed activity in several animal models related to schizophrenia, including induction of c-fos activity in specific brain regions, reversal of deficits in pre-pulse inhibition, and reversal of the effects of MK-801 or PCP on locomotor activity or EEG. This antipsychotic-like profile of GlyT-1 inhibitors in animal models is supported by the initial clinical finding of symptom improvement in schizophrenic patients dosed with the low potency GlyT-1 inhibitor sarcosine as an add-on to their antipsychotic treatment. Taken together, these findings suggest that GlyT-1 inhibitors may be efficacious in the

treatment of schizophrenia, and the Sanofi compound SSR504734 has just entered preclinical development for this indication.

In comparison to GlyT-1 inhibitors, the therapeutic potential of GlyT-2 inhibitors has been less well explored. The main area of interest is pain, since glycine is an inhibitory transmitter in spinal cord, and glycine reduces while strychnine increases hyperalgesia and allodynia in animal models of pain. In summary, the characterization of glycine transporter function and the discovery and development of selective inhibitors for these transporters is a rapidly growing area of research, which may yield important new treatments for psychiatric and neurological conditions.

Glycine Transporters

CURRENTLY ACCEPTED NAME	GlyT-1 (Glycine transporter type 1)	GlyT-2 (Glycine transporter type 2)
STRUCTURAL INFORMATION	638 aa (human) ^a	797 aa (human)
UPTAKE INHIBITORS	Sarcosine (S7672), ^b NFPS (A8977), SSR504734, Org 24598, CP-802,079	Org 25543
TISSUE EXPRESSION	Nervous System, retina, intestine	Spinal cord, brainstem, cerebellum
PHYSIOLOGICAL FUNCTION	Regulation of extracellular glycine levels	Replenishment of neuronal glycine stores
DISEASE RELEVANCE	Schizophrenia, cognitive disorders	Pain, motor disorders

Abbreviations

CP-802,079: ({3-(4-Chlorophenyl)-3-[4-(thiazole-2-carbonyl)-phenoxy]-propyl}-methylamino)-acetic acid

NFPS: N-[3-(4'-Fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine

Org 24598: N-Methyl-N-[3-[4-trifluoromethyl]phenoxy]-3-propyl]glycine

Org 25543: 4-Benzoyloxy-3,5-dimethoxy-N-[1-(dimethylaminocyclopentyl)methyl]benzamide

SSR504734: 2-Chloro-N-[(S)-phenyl[(2S)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide

FOOTNOTES

^a GlyT-1b; other isoforms have slightly different numbers of amino acids.

^b Substrate for transporter.