Glycine Transporters

Key References

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Overview

Glycine is an important neurotransmitter in the mammalian CNS where it acts as an inhibitory transmitter via its interaction with strychnine-sensitive glycine receptors. It can also produce excitatory effects via strychnine-insensitive glycine sites located on NMDA glutamate receptors. The actions of glycine are terminated by reuptake via high affinity glycine transporters. Two distinct types of these transporters, referred to as GlyT-1 and GlyT-2, have been characterized. Both transporters are members of the sodium/chloride-dependent family, which also includes transporters for GABA and for biogenic amines.

In terms of their 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 at least four isoforms (a-d), differing only in their amino terminal sequences, which are transcribed from a single gene via alternative promotor usage and alternative splicing. Although these isoforms vary in their distribution, expression and developmental regulation, there is no evidence that they differ in their functional properties or pharmacology. Multiple forms 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 transporter responsible for glycine reuptake in forebrain areas, and in some regions it may be co-localized with strychnine-insensitive glycine sites on NMDA glutamate receptors. It was originally thought that these sites were normally saturated with glycine, but studies now indicate that glycine transport may keep local synaptic glycine levels very low. This suggests that GlyT-1 could play a physiological role in regulating glutamatergic neurotransmission. In contrast to GlyT-1, GlyT-2 has a predominantly neuronal localization and a more limited distribution, being mainly restricted to the spinal cord, brainstem and cerebellum. Indeed, GlyT-2 appears to be a reliable marker for glycinergic neurons, and is co-localized with strychnine-sensitive glycine receptors. One physiological role of GlyT-2 might be to ensure resupply of glycine to presynaptic terminals. This idea is supported by the findings that GlyT-2 has a different stoichiometry than GlyT-1, and has a much lower capability for reverse transport.

Until recently there have been no potent inhibitors available for either GlyT-1 or GlyT-2, although sarcosine is a low potency, selective GlyT-1 inhibitor. However, the sarcosine derivative NFPS has now been characterized as a potent, selective GlyT-1 inhibitor, which unlike sarcosine, is not a substrate for the transporter. Both NFPS and another GlyT-1 inhibitor, Org 24598, can increase extracellular glycine levels in rat brain. In addition, NFPS has been shown to enhance NMDA glutamatergic transmission in rat hippocampal slices, presumably via increased synaptic glycine levels. These findings indicate that GlyT-1 inhibitors are of potential therapeutic interest for the treatment of schizophrenia. One hypothesis proposes that this disease involves glutamatergic hypoactivity at NMDA glutamate receptors, and clinical trials have shown that administration of glycine itself, as well as other agents with agonist activity at glycine sites on NMDA glutamate receptors, can improve schizophrenic symptoms. Raising synaptic glycine levels with a GlyT-1 inhibitor could mimic clinical effects of glycine agonists and thus provide a new treatment for schizophrenia.

In contrast to GlyT-1, the main therapeutic area of interest for GlyT-2 inhibitors is likely to be pain. Glycine is an inhibitory transmitter in spinal cord, and hyperalgesia and allodynia in animal models of pain can be reduced by glycine and increased by the glycine antagonist strychnine. Although no potent, selective inhibitors of GlyT-2 have been fully characterized as yet, a very recent report suggested that such inhibitors can show analgesic activity in animal models. The development of new potent inhibitors of glycine uptake is likely to stimulate interest in glycine transporter systems and their therapeutic potential.

Glycine Transporters

Currently Accepted Name	GlyT-1	GlyT-2
Structural Information	638 aa (human) [a]	797 aa (human)
Uptake Inhibitors	Sarcosine (S 7672) [b] NFPS (ALX 5407, A 8977) Org 24598 Org 25935	ALX 1393 (A 5475) [c] ALX 1405 [c] Org 26176 [c]

Abbreviations
NFPS: N-[3-(4'-Fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine
Org 24598: N-Methyl-N-[3-[4-trifluoromethyl)phenoxy]-3-phenylpropyl]glycine
Org 25935: cis-N-Methyl-N-(6-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-ylmethyl)amino methylcarboxylic acid

Footnotes

a GlyT-1b; other isoforms have slightly different numbers of aa.
b Substrate for transporter.
c Structures not yet disclosed.