

Glycine Receptor

Key References

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Overview

The amino acid glycine is a major inhibitory neurotransmitter in the vertebrate CNS. Glycinergic synapses are particularly abundant in spinal cord and brain stem, but are also found in higher sensory pathways, including the cochlear nucleus and the retina. The inhibitory actions of glycine are potently blocked by the alkaloid strychnine, a convulsant poison in man and animals. Strychnine poisoning causes disinhibition of motoneurons and leads to hyperexcitability, convulsions and death through respiratory failure. In addition, it produces strong pain syndromes and hyperacuity of visual and auditory responses via disinhibition of sensory processing areas, i.e. dorsal horn of the spinal cord, cochlear nucleus, inferior colliculus and retina.

In addition to its inhibitory postsynaptic action, glycine also acts as an excitatory transmitter. First, it serves as a co-agonist of the NMDA-subtype of excitatory glutamate receptors; second, glycine has been shown to have excitatory effects on embryonic neurons. Like postsynaptic inhibition, this excitatory response is blocked by strychnine and results from an altered chloride equilibrium potential at early stages of development.

The strychnine-sensitive, postsynaptic glycine receptor (GlyR) is a ligand-gated chloride channel protein which mediates inhibition in spinal cord and brain stem as well as in other regions of the CNS. Purification and molecular cloning has shown that in adult mammals the GlyR is an oligomeric transmembrane protein composed of three α and two β subunits. Pharmacologically distinct isoforms of the GlyR originate from the developmentally and regionally regulated expression of four

distinct α subunit genes ($\alpha 1$ - $\alpha 4$). Expression of cloned ligand binding α subunits in *Xenopus* oocytes or mammalian cell lines creates glycine-gated strychnine-sensitive channels, which mimic GlyRs in primary spinal neurons in most of their pharmacological properties and may correspond to extrasynaptic receptors. Coexpression of the structural β subunit modifies the elementary conductance and channel blocker sensitivity of the GlyR chloride channel. In addition, the β subunit is essential for targeting the receptor to the synapse.

The pharmacology of the GlyR has been studied by different approaches. Besides glycine, the endogenous inhibitory amino acids β -alanine and taurine, as well as β -aminobutyric acid, act as full or partial agonists at the GlyR. Their relative potencies, however, differ between the known GlyR isoforms. Agonist activation of the GlyR is enhanced by both neurosteroids and zinc ions. These ligands are thought to be important for modulating the efficacy of glycinergic synapses *in vivo*. In addition, ethanol and anesthetics such as isoflurane and propofol potentiate glycine currents. These compounds constitute the major documented allosteric effectors of the GlyR.

The antagonist pharmacology of the GlyR is still poorly explored. The classical GlyR antagonists, strychnine and its derivatives, still constitute the only high-affinity ligands suitable for GlyR binding studies. In addition, the steroid derivative RU5135, ω -phosphono- α -amino acid (PMBA) and 5,7-dichloro-4-hydroxyquinoline-3-carboxylic acid (an analog of the NMDA receptor glycine site antagonist 5,7-dichlorokynureate), antagonize glycine

responses in cultured neurons and/or cells expressing recombinant GlyRs. Cyanotriphenylborate, a negatively charged structural analog of the cation triphenylmethylphosphonium, has been shown to selectively antagonize GlyR channels created from the $\alpha 2$ subunit. All homo-oligomeric α subunit GlyRs are blocked by picrotoxinin.

Glycine Receptor

CURRENTLY ACCEPTED NAME	Glycine receptor
ALTERNATE NAME	Strychnine-sensitive glycine receptor
RECEPTOR SELECTIVE AGONISTS	Glycine (G 7126) β -Alanine (A 7752) Taurine (T 0625)
RECEPTOR SELECTIVE ANTAGONISTS	Strychnine (S 8753) PMBA (P-204) Cyanotriphenylborate 5,7-Dichloro-4-hydroxyquinoline-3-carboxylic acid
POSITIVE MODULATORS	Neurosteroids Volatile anaesthetics (isoflurane, halothane (H-169)) Propofol Ethanol (E 7023) Zn ²⁺
PERMEATION	Cl ⁻ influx
RADIOLIGAND OF CHOICE	[³ H]-Strychnine

ABBREVIATIONS

PMBA: Phenylbenzene ω -phosphono- α -amino acid