

# Glycine receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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## Abstract

The inhibitory glycine receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Glycine Receptors**) is a member of the Cys-loop superfamily of transmitter-gated ion channels that includes the zinc activated channels, GABA<sub>A</sub>, nicotinic acetylcholine and 5-HT<sub>3</sub> receptors [63]. The receptor is expressed either as a homo-pentamer of  $\alpha$  subunits, or a complex now thought to harbour 2 $\alpha$  and 3 $\beta$  subunits [30, 7], that contain an intrinsic anion channel. Four differentially expressed isoforms of the  $\alpha$ -subunit ( $\alpha$ 1- $\alpha$ 4) and one variant of the  $\beta$ -subunit ( $\beta$ 1, *GLRB*, P48167) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for  $\alpha$ 1 ( $\alpha$ 1<sup>INS</sup> and  $\alpha$ 1<sup>del</sup>),  $\alpha$ 2 ( $\alpha$ 2A and  $\alpha$ 2B),  $\alpha$ 3 ( $\alpha$ 3S and  $\alpha$ 3L) and  $\beta$  ( $\beta$ Δ7) subunits and by mRNA editing of the  $\alpha$ 2 and  $\alpha$ 3 subunit [80, 91, 18]. Both  $\alpha$ 2 splicing and  $\alpha$ 3 mRNA editing can produce subunits (*i.e.*,  $\alpha$ 2B and  $\alpha$ 3P185L) with enhanced agonist sensitivity. Predominantly, the mature form of the receptor contains  $\alpha$ 1 (or  $\alpha$ 3) and  $\beta$  subunits while the immature form is mostly composed of only  $\alpha$ 2 subunits. RNA transcripts encoding the  $\alpha$ 4-subunit have not been detected in adult humans. The N-terminal domain of the  $\alpha$ -subunit contains both the agonist and **strychnine** binding sites that consist of several discontinuous regions of amino acids. Inclusion of the  $\beta$ -subunit in the pentameric glycine receptor contributes to agonist binding, reduces single channel conductance and alters pharmacology. The  $\beta$ -subunit also anchors the receptor, via an amphipathic sequence within the large intracellular loop region, to gephyrin. The latter is a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse [86, 51, 53]. G-protein  $\beta\gamma$  subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop [122, 121]. Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors [94]. Intracellular Ca<sup>2+</sup> appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation [24].

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