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Glycine receptors (version 2020.4) 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, $GABA_A$, nicotinic acetylcholine and $5\text{-}HT_3$ receptors and Zn^{2+}- activated channels. The receptor is expressed either as a homo-pentamer of α subunits, or a complex now thought to harbour 2α and 3β subunits [32, 7], that contain an intrinsic anion channel. Four differentially expressed isoforms of the α-subunit (α1-α4) and one variant of the β-subunit (β1, *GLRB*, P48167) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for α1 ($\alpha1^{INS}$ and $\alpha1^{del}$), α2 (α2A and α2B), α3 (α3S and α3L) and β (βΔ7) subunits and by mRNA editing of the α2 and α3 subunit [82, 92, 20]. Both α2 splicing and α3 mRNA editing can produce subunits (*i.e.*, α2B and α3P185L) with enhanced agonist sensitivity. Predominantly, the adult form of the receptor contains α1 (or α3) and β subunits whereas the immature form is mostly composed of only α2 subunits. The &a;pha;4 subunit is a pseudogene in humans. High resolution molecular structures are available for the α1 and α3 homomeric receptors [49, 19]. As in other Cys-loop receptors, the orthosteric binding site for agonists and the competitive antagonist strychnine is formed at the interfaces between the subunits' extracellular domains. Inclusion of the β-subunit in the pentameric glycine receptor contributes to agonist binding, reduces single channel conductance and alters pharmacology. The β-subunit also anchors the receptor, *via* an amphipathic sequence within the large intracellular loop region, to gephyrin. This 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 [55, 53, 87]. G protein βγ subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop [123, 122]. Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors [95]. Intracellular Ca^{2+} appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation [26]. Extracellular Zn^{2+} potentiates GlyR function at nanomolar concentrations [85]. and causes inhibition at higher micromolar concentrations (17).

Contents

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