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Review

Ethanol effects on glycinergic transmission: From molecular pharmacology to behavior responses

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ABSTRACT

It is well accepted that ethanol is able to produce major health and economic problems associated to its abuse. Because of its intoxicating and addictive properties, it is necessary to analyze its effect in the central nervous system. However, we are only now learning about the mechanisms controlling the modification of important membrane proteins such as ligand-activated ion channels by ethanol. Furthermore, only recently are these effects being correlated to behavioral changes. Current studies show that the glycine receptor (GlyR) is a susceptible target for low concentrations of ethanol (5–40 mM). GlyRs are relevant for the effects of ethanol because they are found in the spinal cord and brain stem where they primarily express the α1 subunit. More recently, the presence of GlyRs was described in higher regions, such as the hippocampus and nucleus accumbens, with a prevalence of α2/α3 subunits. Here, we review data on the following aspects of ethanol effects on GlyRs: (1) direct interaction of ethanol with amino acids in the extracellular or transmembrane domains, and indirect mechanisms through the activation of signal transduction pathways; (2) analysis of α2 and α3 subunits having different sensitivities to ethanol which allows the identification of structural requirements for ethanol modulation present in the intracellular domain and C-terminal region; (3) Genetically modified knock-in mice for α1 GlyRs that have an impaired interaction with G protein and demonstrate reduced ethanol sensitivity without changes in glycinergic transmission; and (4) GlyRs as potential therapeutic targets.

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Abbreviations: GlyR, glycine receptor; LGIC, ligand-gated ion channel; Gβγ, βγ dimer of G protein; TM, transmembrane domain; IL, large intracellular loop domain; GTP-γ-S, guanosine 5′-*O*-(3-thiotriphosphate); GST, glutathione-S-transferase; HEK, human embryonic kidney.

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1. General overview of the neuronal glycine receptor

Neuronal excitability is a complex membrane phenomenon which is also controlled by receptors of the ligand-gated ion channel (LGIC) superfamily, which includes the Cys-loop family composed of the excitatory nicotinic acetylcholine receptors (nAchRs) and serotonin type 3 receptors ($5HT_3$). Upon activation, they undergo conformational changes that increase permeability to cations and increase neuronal excitability. Inhibitory glycine receptors (GlyRs) and γ-aminobutyric acid receptors type A ($GABA_A$Rs), on the other hand, increase membrane permeability to anions, primarily chloride ions, leading to a fast and potent inhibition of neuronal membranes [1,2]. These receptors have a similar structure and can form homo or heteropentameric channels, where each subunit is composed by: (i) a large extracellular amino-terminal domain that provides the neurotransmitter-binding site and has a barrel-like structure formed predominantly by β-sheets accompanied with an alpha-helix in the amino-terminal region containing the ligand binding pocket which is conserved among the different members of LGICs. This neurotransmitter-binding site is located in the interface between two neighboring subunits and involves six regions of the extracellular domain, where the principal face, also called "(+)", is formed by three loops (A–C) of one subunit whereas three β-strands (D–F) of the other subunit contribute to the formation of the complementary face denoted "(−)"; (ii) four transmembrane domains (TM1-4) composed of amphipathic alpha-helices where TM2 contributes to form the channel pore while TM4 is located in the peripheral region interacting with lipid components of the cell membrane [3,4]; (iii) a large intracellular loop domain between TM3–TM4 important for the functional regulation of the receptors, including intracellular trafficking, sorting, insertion into cell membranes, clustering in postsynaptic regions and interaction with intracellular modulators from signaling pathways [5–7]; and (iv) a small extracellular carboxy-terminal region [8] .

Amino acids in TM2 determine the ion selectivity of the pore, thus defining their excitatory or inhibitory nature. For example, the selectivity region is determined by a ring of negatively charged residues in nAchRs, 5HT-3 or positively charged and proline redidues in GlyRs, $GABA_A$Rs [9,10]. In particular, GlyR ion selectivity is controlled mainly by three residues in TM2 (P250, A251, T265) that when mutated change the ion selectivity from anionic to cationic (A251E, T265 V, deletion P250) [10,11]. Indeed, anionic receptors from the LGICs family show a strict permeability to anions with an order of preference for $SCN^- > NO_3^- > I^- > Br^- > Cl^- > F^-$, along with a significant permeability to HCO_3- [12]. From the calculated diameters for each type of receptors (0.7–0.8 nm for the 5HT-3 and nAChRs, 0.5–0.6 nm in the case of $GABA_A$Rs and GlyRs), it has been suggested that partially dehydrated ions are responsible for ion permeation [12].

Several studies have examined the role of the intracellular loop domain and confirmed its involvement in regulating channel conductance by way of positively charged residues acting as a weak filter [13,14]. Mutations in positively charged amino acids at the C-terminal of the intracellular loop domain decreased conductance of GlyRs [15]. Furthermore, this domain was associated to receptor desensitization [16] and ion selectivity involving the electrostatic influence of charged residues [17]. Despite all of these regulatory functions, the intracellular loop domain is not essential for channel formation, and truncated receptors generated functional receptors with macroscopic and pharmacological characteristics rather similar to native receptors [18] .

2. Glycinergic neurotransmission

Glycine is the main inhibitory neurotransmitter in the mammalian spinal cord and brain stem. Activation of GlyRs by glycine leads to a fast increase in chloride conductance which produces hyperpolarization of the neuronal membrane known as an inhibitory postsynaptic potential (IPSP). This phenomenon is associated with a reduction in the excitability and firing properties of the spinal cord and brain stem neurons involved in the control of pain transmission, respiratory rhythms, motor coordination, reflex responses and sensory processing [19–21]. At the spinal and brain stem levels, glycinergic interneurons regulate the generation of action potentials on motoneurons through the presynaptic release of glycine and subsequent GlyR activation [22]. These spinal interneurons also control reciprocal inhibition in reflex circuits producing relaxation of antagonistic muscles during the coordinated contraction of agonist muscles, where Renshaw cells regulate motoneuron excitability by recurrent inhibition through a negative feedback loop [23].

Glycinergic synapses are formed by presynaptic vesicles containing glycine alone or in combination with the neurotransmitter GABA. These neurotransmitters are stored in the vesicles by the vesicular inhibitory amino acid transporter (VIAAT) [24]. Inactivation of VIAAT produces a drastic reduction in GABA and glycine release confirming that glycinergic neurons have a common vesicular transporter with GABA and compete for vesicular uptake in the synaptic cleft [25]. GlyT2, a transport protein responsible for the uptake of glycine from the synaptic cleft, is also found in this region [26,27]. In the postsynaptic membranes, GlyRs are found in the soma and primary processes of inhibitory neurons where their location dynamically changes between synaptic or extrasynaptic distribution, mainly defined by the presence of a microtubule-binding protein named gephyrin that anchors GlyRs in the synaptic cleft [28,29].

GlyRs are composed of α and β subunits that can associate and form homo (5α) or heteropentameric receptors in the conformations 2α-3β or 3α-2β (α/β) which are possibly associated with non- synaptic and synaptic location, respectively [30,31]. Molecular and immunohistochemical studies have described the presence of 4 isoforms of the α subunit (α1–α4) and only 1 β that are found widely distributed in the CNS [32–34]. This diversity is also increased by post-transcriptional modification of the α subunits such as alternative splicing of exons in the α1 [35], α2 [36], and α3 [33] subunits. Also, the receptor undergoes RNA editing, including deamination of cytidines in α2 and α3 subunits [37,38] and post-translational modifications [38,39].

While α subunits are responsible for ion channel formation and contain binding sites for agonists and antagonists, the β subunit is related to structural and regulatory functions such as GlyR clustering in synaptic locations by interaction between intracellular loop domains with gephyrin [29,40], and regulation of the response to agonists or allosteric modulators due in part to the presence of interfaces α/β and β/β [41].

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