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Review

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# The Role of Glycinergic Transmission in the Pathogenesis of Alcohol Abuse

## Rola przekaźnictwa glicynowego w patogenezie nadużywania alkoholu

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## Summary

Alcoholism is a severe social and medical problem. Inadequate ethanol (EtOH) consumption results in acute and chronic conditions, which lead to many hospitalizations and generate considerable costs in healthcare. Alcoholism undoubtedly needs to be thoroughly described, especially in relation to the molecular mechanism of addiction. The current opinion about the pathogenesis of EtOH abuse is mainly based on the dopaminergic theory of addiction, connected with the impaired function of the dopaminergic transmission in the brain's reward system. Moreover, recent evidence suggests that the potential role in alcohol activity is played also by glycinergic transmission, based *inter alia* on inhibitory glycine receptors (GlyRs) sensitive to this simplest amino acid. GlyRs are pentameric, ionotropic receptors from ligand-gated ion channel family and facilitate membrane permeability to chloride ions. The receptors are widely present in the human body and spread to the peripheral and central nervous system, where they are engaged in several processes, especially in the regulation of nociception, movement control and, possibly, also they are responsible for controlling the brain's reward system involved in the pathogenesis of addiction. The last localization seems to be really important and consists of a new insight into the search for novel substances to prevent or cure the consequences of EtOH abuse. In this paper describes recently discovered and animal-tested ligands, which may be an interesting tool in the treatment of alcohol-related syndromes.

**Keywords:** **Ethanol • Addiction • Glycine Receptors**

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## INTRODUCTION

Ethanol (EtOH) is undoubtedly the most commonly used recreational substance whose consumption results in acute and chronic consequences [24]. It produces acute intoxication and constributes to all the incidents connected with it, especially injuries, car accidents and suicide behaviour. Delay consequences of harmful drinking encompass EtOH psychoses (e.g. Otello's syndrome, Nut alcohol hallucinosis, Korsakoff amnesia) and neurological disorders, for example, avitaminosis leading, *inter alia,* to disruption of mammillary bodies and posterior column ataxia [9]. Psychiatric disturbances associated with alcohol consumption lead to 1,989 deaths per year in Poland and, furthermore, this count is systematically increasing [22]. Based on such data, alcohol consumption appears as one of the main problems in public health. This term also contains social and the familiar negative consequences of drinking [22, 25]. Currently, in medicine there is a period of stagnation in the treatment of alcohol disturbances. The commonly used medication regimens (including acamprosate, disulphiram, or cognitive therapy) do not always have successful results, so there is an urgent need to search for a new insight into the pathogenesis and molecular basis of EtOH addiction, taking into account the role of other neurotransmitters than dopamine, like glycine.

Dopamine (DA) is the main neurotransmitter involved in the processes of addiction behaviour. Synthesized in the substantia nigra (SN) and ventral tegmentum area (VTA), dopamine plays a key role in neuronal junctions between the brainstem, striatum, limbic system and cerebral cortex [1]. These specific connections form the brain's reward system, regulating motivational behaviour (for example, drug seeking and drug taking, despite negative health consequences).

DA action is a direct consequence of stimulating D1 and D2 receptor families, among which D2 is represented by two isoforms as a result of alternative splicing (D2L and D2S). Both types, D1 and D2, differ in affinity to DA, among them the D2 receptors with high ability to bind DA are thought to act mainly in "firing" DA release (indicating reward);

on the other hand, D1, with lower affinity, is considered responsible for low concentration tonic DA impulses [15]. Dopaminergic connections between VTA and nucleus accumbens (NAcc) are thought to be affected by chronic alcohol consumption [29]. Evidence suggests that the common denominator for EtOH abuse and other drug addiction is the disruption of dopamine signalling in the mesocorticolimbic tract [13].

## GLYCINE RECEPTORS: OCCURRENCE, MOLECULAR STRUCTURE AND ACTION

Inhibitory Glycine Receptors (GlyRs) are widely spread among the peripheral and central nervous system, especially in the spinal cord and brain stem; however, their occurrence in VTA, a structure of CNS thoroughly associated with the pathogenesis of addiction, has been also confirmed [21]. Despite the variety of localizations, the function of this group of receptors remains still relatively unknown. These receptors were discovered in 1973 by Young et al. as a result of confirming the strychnine-binding mechanism to postsynaptic ion channels [33]. Stimulation of these groups of proteins induces chloride influx into the axoplasm and results in the hyperpolarization of the neuron and, as a consequence, the inhibition of signal conduction. Apart from strychnine, more compounds affecting the function of GlyR were described, with EtOH being among them [31]. The main physiological ligand-glycine is the simplest amino acid, which could be replaced with other similar ones, like alanine, threonine, taurine or serine - acting as agonists. Furthermore, one of the commonly used ingredients of food additives, caffeine, is the most recognizable antagonist of this receptor, which partially (with the exceptionof the theory of phosphodiesterase inhibition) explains the mechanism of the stimulating role of methylxanthines [10].

GlyRs are pentameric, ionotropic receptors connected with cell membrane permeability to chloride ions and with the exception of GABA receptors, they seem to play an enormous role in providing balance between excitatory and inhibitory types of neurotransmission [32].

The mechanism of GlyRs action is based on their combined molecular structure, common for all proteins, for the I Ligand-Gated Ion Channels (LGIC), belonging to the Cys-Loop superfamily [33]. Membership in the LGIC family suggests a very important neurophysiological role of these proteins, *per analogiam* to 5HT-3, nAChR and $GABA_A$ also belonging to these groups [19]. For each GlyR purified protein form there are three species of polypeptide: $GlyR_\alpha$, $GlyR_\beta$ and gephyrin, which anchor the channel to the postsynaptic cytoskeleton and also interact with other parts of the GlyR. It was shown that every receptor subunit is coded by an adequate gene: GLAR1-4 and GLARB (encoding β subunit). Functionally, this polypeptide is divided into a N- terminal extracellular domain (acting as the ligand binding site), four transmembrane segments (Called TM1-TM4), intracellular loop and extracellular C-terminus [11].

The transmembrane domain plays a key role in chloride ions permeability. Built up of four α-helix structures (including arginine, glycine and threonine, lining the inside of the pore), during ligand binding to the extracellular domain, induces conformational change (rotation of TM2 segment), which enables $Cl^-$ influx [11]. Plethora modulators of the GlyRs (neurosteroids, alcohols and anesthetics) interact with the transmembrane domain in a place called the "big cavity". Polar amino acid residues which are present in the aforementioned cavity are thought to be responsible for the effect of high EtOH dose. The role of each GlyR subunit in the central nervous system is summed up in Table 1. Mutation of GLRA1 gene encoding Gly receptors has been

confirmed to have clinical significance, resulting in *stiff baby syndrome*, connected with the hyperexcitability of motoneurons and the dysfunction of inhibitory Renshaw cells [2].

## ROLE OF GLYCINERGIC TRANSMISSION IN ETHANOL ABUSE

Experiments conducted by Celentano and colleagues revealed that exposure on 50-100 mM EtOH results in forcing chloride influx via GlyRs during *in vitro* studies [7]. Moreover, in mice with a transgenic mutant glycine receptor decreased alcohol sensitivity was observed. [14]

In this study, introduction of mutation S267Q subunit α in the structure of the studied receptor has caused better scores in mice assessed by rotarod, alcohol inhibition of strychnine seizure and loss of righting responses, which, according to authors, confirmed the hypothesis that glycine receptors not only *in vitro* but also *in viv*o effect post-EtOH behavioral changes in animals. GlyR affinity to EtOH depends on the neurodevelopmental state has been also highlighted in this study - embryological GlyRs combined from α2 subunits were less sensitive to alcohol modulation [12]. Taking into account the aforementioned evidence, mechanisms of interaction between EtOH and GlyR are promising, and thus should be thoroughly investigated.

There are a variety of theories aiming to describe such a phenomenon. The most suitable one is the theory of direct acting or indirect-acting on the receptor's compound: the first is connected with the role of EtOH pocket consisting of amino acid residues between TM2 and TM3 parts of the transmembrane domain; also, TM4 seems to play an important role in alcohol binding via forming a hydrophilic cavity [5]. It is thought that this kind of mechanism is responsible for modulation by means of high concentrations of EtOH (200 mM) [14]. A second theory refers to an indirect interaction, based on the role of G-protein (GP). EtOH at lower concentrations is supposed to affect intracellular mechanisms of transduction, especially by a sub-membrane α1 subunit of GlyR and βϒ subunits of GP [14].

Extrapolating these molecular mechanisms into brain structures engaged in alcohol abuse has proved that glycinergic transmission appears to play an enormous role in preventing the process of Long-Term Potentiation of GABA neurons in VTA - main structure connected with drug addiction [6]. The effect is confirmed both, *in vivo:* animals administered with glycine into the VTA exhibited reduced alcohol consumption during 24h [6], and *in vitro*: naïve VTA neuron cells in *vehiculum* with glycine 10 μm after 15 min reduced the intensity of LTP process [6]. Another part of the brain's reward system marked with glycine receptor is the nucleus accumbens (NAcc). Receptors are not only present in NAcc, but they also regulate dopamine release [16]. In a study by Molander et al., local strychnine (competitive GlyR antagonist) influx prevented over-releasing of dopamine and increased alcohol consumption in tested animals [23].

## PHARMACOLOGICAL PRINCIPLES OF GLYR

The severity of acute and chronic consequences of EtOH abuse create an urgent need to search for drugs that may be used to prevent and treat para- alcoholic syndromes. GlyRs appear to be a novel target in pharmacotherapy. Based on previously obtained evidence connected with the clue role of Gβγ protein dimer in interaction between EtOH and GlyR [27], San Martin and colleagues in their studies aimed to find the molecule, which could

**Table** 1. Role of each GlyR subunit in CNS

| Subunit of GlyR | Role in the Central Nervous System |
|---|---|
| α1 | Inhibitory role in Spinal Cord, mutations result in hyperexcitability of motoneurons and stiffness syndromes |
| α 2 | Mainly expressed in embryonic and neonatal life, then replaced by α1 |
| α3 | Expressed in Rexed's laminae I and II in the Spinal Cord- inhibition of nociceptive signal conduction |
| α4 | Intellectual disability, behavioral problems, facial abnormalities |
| B | Inhibitory role in spinal cord and brain stem. Mutation results in *spasmodic* animal syndrome |

be able to bind with the aforementioned structure and, as a consequence, reverse the effects of acute alcohol intoxication by inhibiting glycine current. In 2012, the researchers discovered that a small, seven-peptide molecule (QRH(C7)) is able to bind to Gβγ protein and inhibits EtOH induced reinforcement. Moreover, using in silico analysis with molecular dynamics and docking, they revealed a region responsible for binding this peptide composed of aspartic acids residues in 186, 228 and 246 positions [27]. Obtained data served as a basis to identify more compounds, which potentially could take part in attaching with Gβγ. Thirteen molecules were synthesized and tested in vitro and in vivo [28]. For *in vitro* testing, San Martin et al. used HEK293 cells with forced GlyRα1 expression, which were administered with previously acquired molecules. Using the patch clump technique differences, the evoked currents were assessed after 1 min and 15 min after the introduction of peptides: M554 and M890 (Results explained in Fig. 1).

In the first step, cells with M554 and M890 (200 μM) did not express a significant difference in glycine currents between 1 and 15 minutes without EtOH, which suggests that the aforementioned compounds did not affect the chloride influx through the glycine receptor directly (Fig. 1 A). In the second probe, it was proven that M554 and M890 decreased EtOH- induced chloride current via GlyRs (Fig. 1B). By in silico modelling it was also confirmed that the used peptides interact with asparagine residues in βγ subunits. Next, the research group decided to examine whether small molecules also have an affect on the spinal cord cells, without forced GlyR expression, in this stage, molecules occurred to inhibit EtOH- induced postsynaptic glycinergic current in spinal neurons (Fig. 1C). The aforementioned results confirmed suspicions that the peptides inhibit EtOH potentiation in recombined and native cells. The further procedure, demonstrated in Fig. 2 included *in vivo* testing with C57BL6/J mice. At first, locomotor functions and their ability to explore were assessed after i.p. administration of 1.0 g/kg EtOH. In this model, the animals increased their locomotor activity (measured by open field assessment), but this symptom was not affected by M554 (Fig. 2A). Taking into account the higher doses of alcohol (2.0 g/kg), locomotor activity was assessed using accelerating rotarod assay. As a consequence of administering M554, it was observed that these animals recover faster from incoordination caused by EtOH (Fig. 2B); the effect was not significant for M890. Moreover, for M554 the sedative effect of EtOH (3.5 g/kg), measured by Loss of Righting Reflex time (LORR) was reduced (Fig. 2C). Interestingly, the effect of M554 was the highest for 50 mg/kg in comparison with 100 mg/kg and 200 mg/kg, the last one having no effect, which the authors explained based on a probable aspect of decreased solubility of the peptide in higher concentrations. Alcohol blood concentrations, measured 30 min after EtOH injection, did not show any significant differences, which may suggest other causes of this effect due to forced clearance or metabolism.

From the cited publication, it could be claimed that Gβγ protein, associated with GlyR also in animal model, seems to be responsible for the effects of acute alcohol intoxication, but in higher concentrations (2.0-3.5 g/kg), since the euphoric effects in the dose of 1.0 g/kg are not significantly reduced by peptides inhibiting the aforementioned structure [28].

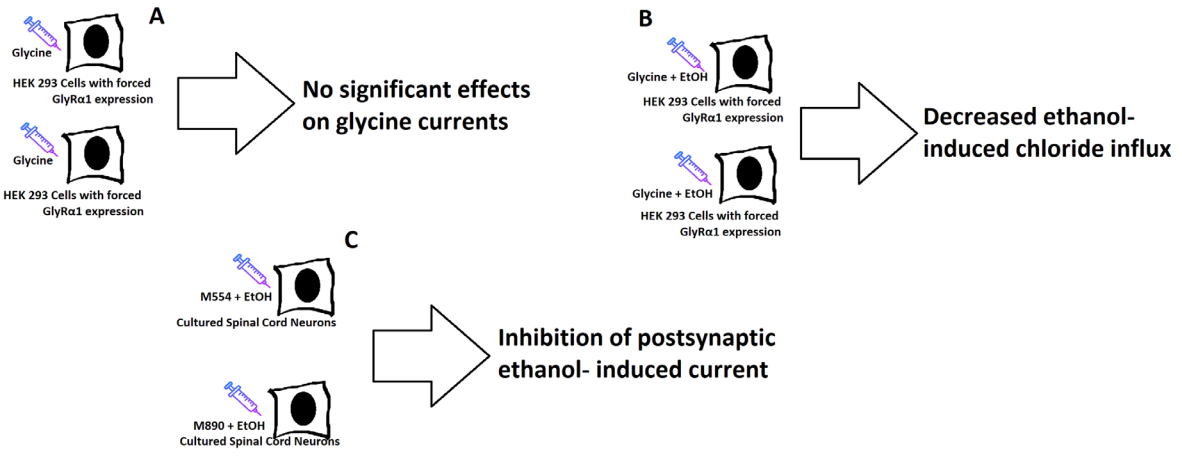


**Fig. 1**. Inhibition of ethanol- induced GlyR potentiation; A - cell culture without EtOH, B - cell culture administered with EtOH, C - reduced ethanol action on spinal cord neurons

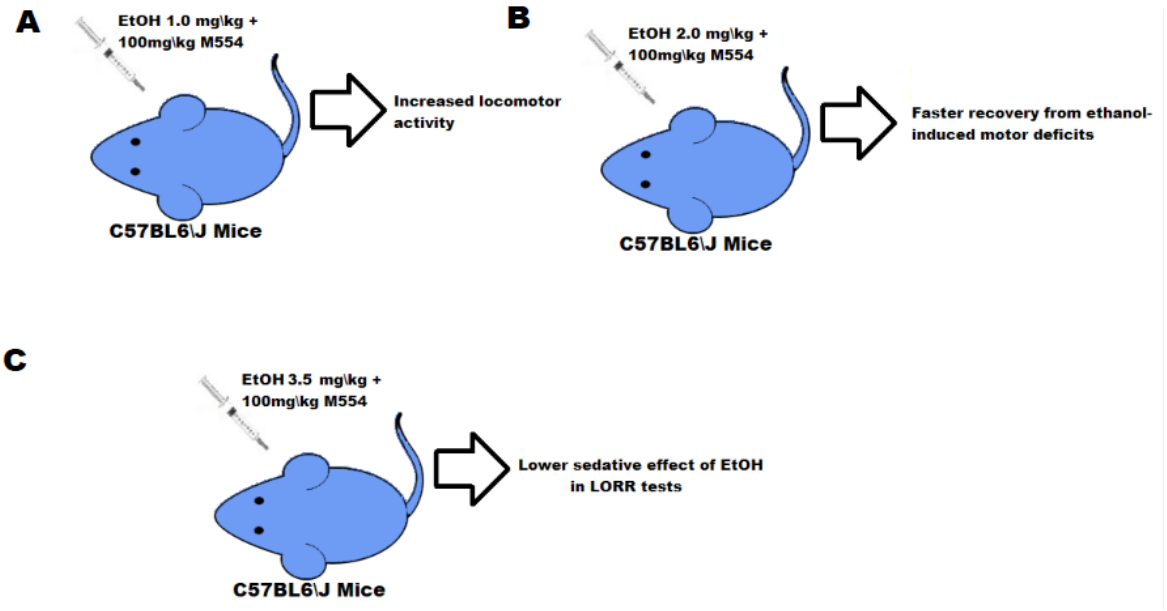


**Fig. 2**. Effects of M554 in animal model; A - no significant effect on locomotor activity after EtOH, B - mice assessed by rotarod test recovered faster from motor incoordination, C - decreased sedative effect of EtOH

## ANOTHER IMPORTANT ASPECT OF GLYCINERGIC TRANSMISSION

With the exception of the specific receptors described above, glycine is engaged in more types of neurotransmission, especially in glutamatergic pathways. In the case of EtOH addiction, the role of NMDA receptors (NMDAR) is really worth the attention.

NMDAR are membrane ion channels, mainly built up of NR1 and NR2 subunits and stimulation of this structure, regarding agonist (glutamate) or co-agonist (glycine, serine) binding, results in calcium ions influx. In the nineties, it was proven *inter alia* by Rabe & Tabakoff that EtOH affects NMDAR in cell culture and they revealed that glycine in a concentration of 10μM decreased the inhibitory activity of alcohol on the calcium current via the NMDAR [26]. This specific outcome suggested a hypothesis about the affinity of EtOH to the "glycine place" in NMDAR (non-sensitive for strychnine), which for example was confirmed on Xenopus oocytes (cell model for ion channel investigations) [4] and in vivo [20]. It was shown that mice expressing receptors with reduced affinity to glycine (Grin1(D481N)) exhibited lower motor impairment and anxiolysis following EtOH administration in comparison with wild-type [20]. The use of an animal model furthermore indicated a probable mechanism of increased impulsivity due to excessive alcohol consumption, as a recent article by Irimia and colleagues [18] proved decreased disturbances in five-choice serial reaction time task (specific paradigm used in impulsivity assessment in rodents) after injection of ALX5407 (glycine transport inhibitor which leads to change a NMDA glycine site availability) into ventromedial prefrontal cortex in rats. Based on the collected data, it could be thought that glycine place in NR1 subunit of NMDAR seems to have a crucial role in the pathogenesis of behavioural changes following alcohol addiction and is an important target in research, aiming to describe the pathogenesis of alcohol encephalopathy.

Another interesting direction in glycinergic transmission is the system of aminoacid transporters, especially GlyT1 and GlyT2. Their role among inhibitory synapses is based on controlling the glycine concentration in extracellular space. Discovery of the GlyTs role was a new insight into the pathogenesis of mental disorders and resulted in many new investigations connected with the search for new drugs, such as bitopertin for schizophrenia [30], which achieved even the third phase of clinical trials. Focusing on alcohol, GlyTs are engaged in mesolimbic signalling, since it was revealed that Org 25935 (GlyT1 inhibitor) reduced the compulsive preference of EtOH drinking in rats [17].

## NEUROPHARMACOLOGICAL CIRCUIT OF REWARD

Summarizing all the above mentioned results, researchers came to the conclusion about the existence of a specific neuropharmacological circuit in reward system, built up of connections between four types of neurotransmissions: glycinergic, gabaergic, dopaminergic and cholinergic. The last type of transmission is based

on connections between the brain stem nuclei (pedunculopontine and laterodorsal tegmental), which send cholinergic fibres into VTA and seem to have probably an excitatory effect on DA release in this brain structure by stimulating nAChRs [3], but on the other hand dopamine outburst is inhibited by GABA-ergic neurons from NAcc.

The glycinergic transmission described in this article plays a key role in stopping GABA outputs and, therefore, also disinhibiting the release of dopamine in VTA. Such a kind of circuit explains interactions between EtOH-consumption and glycine receptors, especially when it was confirmed in animal studies on alcohol medium- and high- preference rats [8], as it was discovered by Chau and colleagues that acamprosate-induced reduction of drinking could be reversed by local injections of strychnine (GlyR antagonist) into NAcc.

## CONCLUSIONS

Expression of glycine signalling among structures of CNS, engaged into the pathogenesis of alcohol abuse syndromes, constitutes a relatively new insight into the EtOH-addiction problem. Growing evidence of glycine neurotransmission in NAcc, VTA and other parts of reward system invite another thorough investigation of the molecular aspects of mesolimbic dopamine pathway, especially when the current achievements result in obtaining particles interfering with EtOH and GlyRs via intracellular cascades of signalling- Gβϒ protein. Although the knowledge in this field is growing, evidence of GlyRs involvement EtOH-addiction problems presented in this paper clearly indicates an urgent need to investigate more compounds acting via this pathway and testing them in animal models of alcohol dependence receptors.

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