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Review

Glycine receptors: Structure, function, and therapeutic implications

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ABSTRACT

Glycine receptors are considered as an integral part of higher brain function in mammals. The main function of glycine receptor is fast inhibitory transmission brought about by glycine neurotransmitter, its full agonist. This receptor is part of the glycinergic system which controls key physiological functions such as motor coordination, regulation of the rhythm of respiration and pain signalling. Glycine, a non-essential amino acid, causes hyperpolarisation within the glycine receptor, leading this ion channel to open and allow influx of chloride ion. The glycine receptor is found within the central nervous system and peripheral nervous system. It has also been found within amacrine cells, as well as renal medulla and cortex. The glycine receptor is a pentameric ligand-gated channel, part of the Cys-loop superfamily. It is composed of large ECD, C terminus, transmembrane domain M1-M4, and a 4α:1β glycine receptor subunit stoichiometry. The glycine receptor can be found as either homomeric or heteromeric subtypes. Alpha subtypes are crucial for important physiological functions such as breathing control and nociceptive system processing while the beta subunit aids in glycine receptor clustering and synapse stabilisation with its interaction with gephyrin scaffold protein. When hyperpolarised, the receptor transitions between close, open, and desensitised states. Factors that affect the activity and function of glycine receptors are gephyrin, ivermectin, strychnine and picrotoxin while certain endogenous modulators include partial agonists, positive allosteric modulator, antagonists, and bidirectional modulator are used for pharmacological modulation. Further studies need to be carried out on how glycine receptors are also implicated in chronic pain and nociception, epilepsy, autoimmune diseases and hyperekplexia.

1. Introduction

The achievement of the current level of sophistication obtained by the mammal body is no small feat but an obvious illustration of the driving power of evolution. Humans can be considered at the forefront of mammalian evolution due to their high brain function. Such evolution in mammals has allowed for the human body to work like a well-oiled machine whereby the cells that make up the body are in constant communication with each other, and this is efficiently facilitated by receptors. Cellular receptors are considered one of the main communication messenger systems of the cells and one of the most notable receptors being the glycine receptor.

1.1. What is a glycine receptor?

Glycine receptors (GlyRs) are proteins which act as pentameric ligand-gated channels, through which ions can pass. GlyRs are permeable to the chloride ion which is allowed to pass through the pore found in the channels upon the inhibitory effect of glycine, a neurotransmitter (San Martin et al., 2022).

Neurotransmitters, such as glycine, acts as messengers of a chemical nature and they are secreted by different neurons found in the brain. These neurotransmitters are responsible for nerve impulse propagation from one neuron to another. With chemical messengers, the information is effectively and accurately sent to the targeted site and the desired effector organ is enabled and specific functions could be carried out. The various types of neurotransmitters would determine the neurotransmitter system and this in turn would have a specific role to fulfil within the nervous system itself. The compartmentalisation of different neurotransmitter systems, each with different roles, is paramount for ensuring harmonious sustenance of healthy behavioural and physiological body functions (Nimgampalle et al., 2023). Both the glycine receptor and glycine neurotransmitter make part of the glycinergic neurotransmitter system. Glycine, an amino acid, binds to the glycine receptor, causing the opening of the pore that is chloride-permeable which upon the movement of chloride ion would lead to shift towards

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a more negative membrane potential, also known as hyperpolarisation (San Martin et al., 2022). According to (Marchetti et al., 2022), the interactions between ligand and the receptor, as is the case for the glycine receptor, is crucial to activate signal transduction that is intracellular. It was also stated that such interactions are also important due to their ability to allow the precise definition of the dynamics of the interaction. This means that efficiency of the glycine receptor would directly influence the outcome of what occurs within the cell itself. Furthermore, it would also indicate that any damaged glycine receptors would consequently lead to a reduction in cell hyperpolarisation which could have certain serious implications.

1.2. What is the function of glycine receptor?

A glycine receptor is responsible for the mediation of the central nervous system's fast inhibitory signalling. This signalling mainly translates to locomotion regulation by GlyRs, which are widely found distributed in both the brainstem and the spinal cord (Zhu and Gouaux, 2021). The activation of GlyRs is what controls functions of a neurophysiological nature that are regarded as key functions. These include motor coordination, respiratory rhythm and even muscle tone (San Martin et al., 2022). Glycine receptors also have a very crucial role in transmission of pain signalling and excitatory signal counterbalancing (Zhu, 2022).

1.3. Why is it important in terms of neurobiology?

Glycine receptor plays a major part in neurotransmission for the nervous system. This receptor, with the help of glycine as its neurotransmitter, allows communication between neuronal cell through signal transmission (H. Yu et al., 2021). The relevance of glycine receptor and its existing subunit types, in terms of neurophysiology, is related to health and disease. Any genetic alterations made to the GlyR may lead to pathologies linked to neurophysiological well-being (San Martin et al., 2022). According to Zhu and Gouaux (2021), with GlyRs whose function is locomotion regulation and behaviour, any mutations to such receptors would underpin a neurological locomotion disorder such as startle disease. There are some neurological disorders that are also associated with the GlyR defects including implications in autism spectrum disorders and hyperekplexia. Since these diseases are a direct result of any dysfunction of the glycine receptor, any of the GlyR activity-modifying compounds may hold significant therapeutic potential (Zhu, 2022).

2. Context of glycine receptors

2.1. Location

Glycine receptors are described as being part of a group of neurotransmitter receptors that are distributed the most widely in the central and peripheral nervous system Fricke et al. (2023). According to Maynard et al. (2021), it is the GlyRs that are the main receptors of fast-inhibitory neurotransmission primarily found within the adult brainstem and the spinal cord. It is in these areas, where these networks of inhibitory glycinergic systems are found, that are important for regulation of both sensory and motor processes. However, there is a distinction between the GlyRs found in adults and those found in embryos. According to Salceda (2022), in the developing brain, glycine receptors are functionally found in almost all areas, unlike in adulthood, where glycinergic neurotransmission and the glycine neurotransmitter, with its important role, is limited to a few areas of the brain, including the retina and the spinal cord. Evidence suggests that glycine, with the aid of GlyRs, plays a role in central nervous system (CNS) development. The glycine receptors, in early development, are expressed in migratory neurons and dorsal progenitors. These structures then contribute to the migration of the cells, development of morphology and control of the cell cycle.

2.2. Distribution

The specific distribution and location of the inhibitory glycinergic neurons in the spinal cord would correspond to either the mediation of sensory information in the dorsal spinal cord or mediation of motor information in the ventral spinal cord (Maynard et al., 2021). Both areas, regardless of overseeing either motor or sensory information mediation, require high fidelity and reliability of transmission. Thus, with GlyRs being part of such glycinergic neurons, their position in the spinal cord would influence what type of information is relayed and transmitted through these receptors. In terms of the spinal cord, this difference in function and distribution of GlyRs found in glycinergic neurons, is due to a difference of type of embryonic origin. This is what leads the various specific neuron types to reside in characteristic spinal cord layers (Maynard et al., 2021). That being said, this study, through a combination of quantitative techniques such as molecular counting and imaging techniques such as 3D-electron microscopy and single molecule PALM imaging, illustrated differences in GlyRs distribution in the spinal cord. In the ventral horn GlyRs of spinal cord differs from the dorsal horn by having double the number of total copy numbers, more convoluted receptor morphologies and even larger postsynaptic domains. However, the result also showed that the GlyRs that are endogenous exhibit packing density that are constant around 2000 GlyRsμm^{-2} across spinal cord synapses. Furthermore, the postsynaptic strength of glycinergic neurotransmission, for both sensory and motor in the spinal cord, is dependent on the size and morphology of inhibitory postsynaptic specialisations and not on the differences in packaging of the GlyRs (Maynard et al., 2021).

Certain studies stated the presence of glycine receptors in mammalian retina of mice, (Sawant et al., 2021; Perez-Leon et al., 2022). According to Sawant et al. (2021), there is the presence of a synapse that is mixed, one that contains both glycine and GABA receptors (GABA-glycine receptor synapse). These synapses are found on retinal ganglion cells (RGCs) found in the mammalian retina. In the retina the inhibition is carried out by both GABAergic and glycinergic system on amacrine cells and across the ON-sustained alpha RGCs, there are post-synapses containing, specifically, both GlyRα1 and $GABA_A$α3 receptors (mixed receptor). The study also highlighted how glycine and GABA neurotransmitters are released from dual presynaptic sites on amacrine cells. The glycine receptors on the RGC are preceded by the GABA receptor and there is a correlation between the receptors. This is so because if there is no early expression of GABA receptor, then the recruitment of glycine receptors is impeded.

The study conducted by Perez-Leon et al., (2022), also demonstrates that both GABA and glycine neurotransmitters are released from a subpopulation of amacrine cells of the mammalian retina of mice. These

neurotransmitters are co-released due to the presence of glycinergic neurons' co-expression of GABA transporters and GAD67 in the mouse retina. The postsynaptic neurons, found neighbouring this amacrine neuron subpopulation, contained receptors for both glycine and GABA. This study also illustrated that it is the GABA and glycine transporter 1 (GlyT1) that determine dual phenotype, whereupon the same vesicular transporter recognises glycine and GABA for vesicle refilling. This study also proposed that under differing intensities of light, the amplitude and duration of the inhibitory signal, that is relayed onto the ganglion and amacrine cells, is strengthen by the co-release of glycine and GABA transporters and neurotransmitters. Under hyperexcitability of the synapse, the corresponding kinetics of GABA and glycine allows the signal of excitation inhibition to be prolonged and be faster, respectively,

The glycine receptor is made up of both beta and alpha units and one of these subunits is the glycine receptor alpha 3 (GLRA3/GlyRα3) in the central nervous system (CNS). In a recent study, it had been stated that prior evidence based on the mapping of mouse glycine receptor alpha 3 (Glra3) and human GLRA3 by the Human Protein Atlas correlated with the results of their study on the glycine receptor alpha 3 in mice. The Human Protein Atlas revealed that this GLRA3 has been found, in humans, in the amygdala, thalamus, cerebral cortex, hypothalamus, basal ganglia, brainstem (medulla oblongata and pons), hippocampal formation and midbrain. In mice, this receptor type has also been located in the same areas in humans but also in cerebellum and olfactory bulb. In the results of this study illustrated that highest Glra3 expression was found in the hypothalamus, amygdala, cortex and striatal regions of the mice's CNS. However, with the aid of bulk-quantitative real-time-PCR analysis, expression of glycine receptor alpha 3 was found also in the thalamus, hippocampus, pituitary gland, spinal cord, brainstem and cerebellum. Furthermore, the study also highlighted how there an overall higher Glra3 expression in all the mentioned areas of male mice brains, in comparison to the brains of female mice (Ceder et al., 2023).

Glycine receptors, glutamate receptors and GABA receptors along with respective enzymes and neurotransmitters, which are all tools in GABA metabolism and synthesis are also present in the renal cortex's vascular and tubular compartments as well as the medulla. The role of glycine, aided by glycine receptors, aids in signalling of renal blood flow through vasoactivation (Wildman et al., 2023). Table 1 illustrates a summarised table of the function, location and distribution of GlyRs.

Table 1
Summary table of showing function, location, and distribution of the GlyRs.

Function of GlyRs	• Fast inhibitory neurotransmission by permeation of chloride ions through the receptor in adult spinal cord and brain stem (Maynard et al., 2021) • Aids in embryological development of CNS (control of cell cycle, migration of neurons and development of morphology) (Salceda, 2022)
Location of GlyRs	• Central nervous system (brain stem and spinal cord) (Fricke et al., 2023) • Peripheral nervous system (Fricke et al., 2023) • Co-exitance with GABA receptors in retina of mammals (Sawant et al., 2021)
Distribution of GlyRs	• Embryonic origin of GlyRs affect function of GlyRs in spinal cord (Maynard et al., 2021) • In mice amacrine cell, GABA and glycine receptor co-exist (mixed synapse) on synapse and their respective neuro-transmitters co-released from dual-presynaptic sites (Sawant et al., 2021; Perez-Leon et al., 2022) • In mice, α3GlyR expression was found highest in hypothalamus, striatal regions, amygdala, and cortex (Ceder et al., 2023) • Found in medulla and renal cortex to aid in regulation of blood flow (Wildman et al., 2023)

3. Molecular structure and function

3.1. Glycine as an amino acid

Glycine is described by Imenshahidi and Hossenzadeh (2022), in their review, as being a very major and important amino acids used by the human body and the simplest in terms of structure. The main sites of glycine generation within the human body are the kidney and the liver where it is used to produce purine, collagen, glucose, and creatine. The results from this review stated how *in-vivo* glycine, meaning glycine that is produced inside the body is not sufficient for the needs of the human body to be met and the plasma concentration of glycine is decreased in patient with metabolic syndrome. This syndrome was described by Imenshahidi and Hossenzadeh (2022) as a condition where a patient presents with an array of factors such as dyslipidaemia, abdominal obesity, insulin resistance and hypertension. The conclusions obtained from this review were that improvement of factors of metabolic syndrome would improve should there be glycine supplementation.

According to Aguayo-Cerón et al. (2023), their review article noted how, for mammals, the amino acid glycine, is also described as a non-essential amino acid because it is endogenously synthesized for the body by glyoxylate serine, threonine, and choline. Glycine was also described as crucial for its role in many biomolecules' synthesis such as purine and creatine nucleotides. This amino acid is also known as amino acetic acid. It was also recorded in this review that there have been many previous studies that focused on the ability of glycine to decrease free fatty acid concentrations in order to improve the response of insulin and also decrease cytokines that are pro-inflammatory as well as mediate other changes. Aguayo-Cerón et al. (2023), emphasized that in many cells, nuclear factor kappa B (NF-κB) expression is modulated, and it is during this modulation that glycine exerts its anti-inflammatory effects. What is more, dietary supplementation of glycine was also mentioned as being crucial in order to avoid chronic inflammation development.

There are many effects that glycine has over the body (Fig. 1). The ability of glycine to cause amelioration of motor deficiencies after a surgical intervention is why motor function control is associated with glycine. It also has a role protein configuration, pain transmission and gene expression regulation along several other biological functions. Glycine was also reported to aid in muscle tone improvement, delay degeneration of muscle, restore tissue hence it has a role in the formation of scar. It also modulates growth during growth hormone synthesis regulation acts as act as an antacid and synthesises collagen (Aguayo-Cerón et al., 2023).

In their article, Shahsavar et al. (2021) describe glycine as having a dual role within the CNS. One of the two roles is glycine's ability to cause an influx of chloride ions, through hyperpolarisation, by way of the ionotropic GlyRs, which are located at postsynaptic terminals of neurons. This role of glycine, in the inhibitory glycinergic synapses, would characterise glycine as a classical functioning neurotransmitter. The secondary role of glycine is its ability to modulate, in a positive manner, plasticity and neuron-excitation, that is calcium dependent, of glutamatergic synapses. This occurs because there is obligatory co-agonism of glycine with the *N*-methyl-$_D$-aspartate (NMDA) receptor. Homeostasis of glycine is maintained by reuptake glycine transporters 1 and 2 (GlyT1 and GlyT2).

3.2. Structure of glycine receptor

The glycine receptor is composed of one beta (β) subunit and four isomers of alpha (α) subunits (α1, α2, α3, α4). There are also four transmembrane domains (transmembrane domains M1-M4), a short

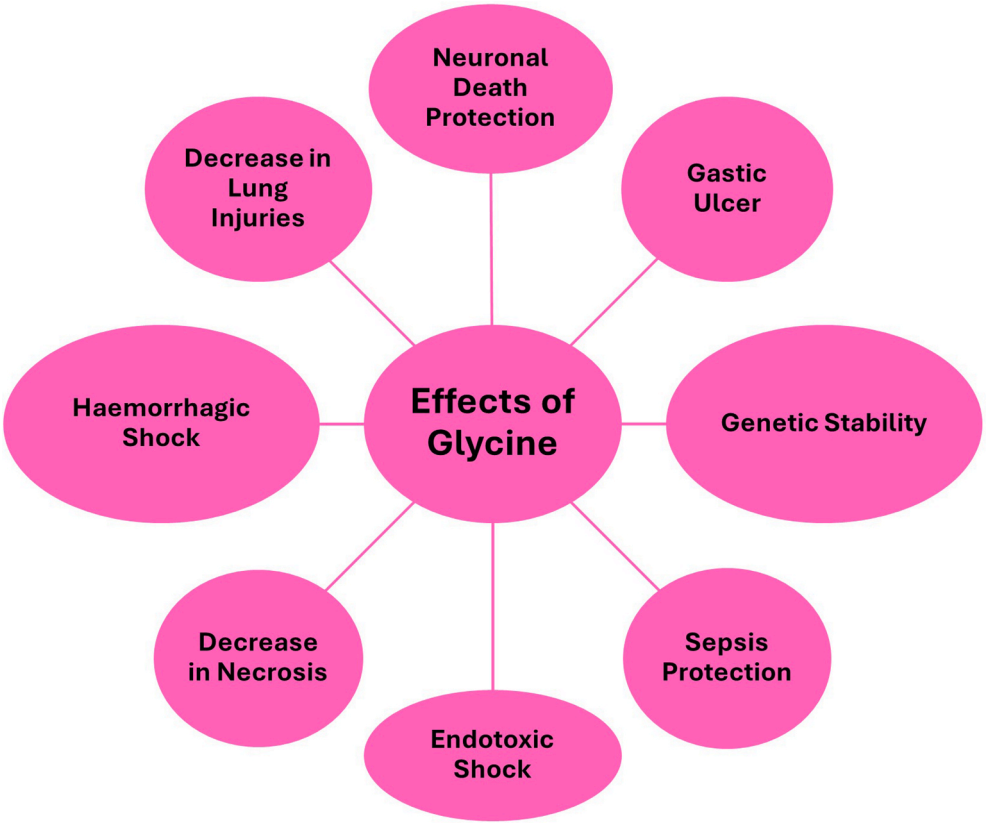

Fig. 1. The various effects of glycine.

extra-cellular C-terminus and a large extracellular domain (ECD) connected to each subunit (Wiessler et al., 2024). The transmembrane domains M3 and M4 are connected to each other through a long intracellular loop and the ECD contains binding pockets that are a result of two subunits that are adjacent to each other extracellular domain (Zhu, 2022). Together, a pentameric ligand-gated channel (pLGICs) which involves chloride forms from these subunits, which is termed a glycine receptor. GlyRs make part of the Cys-loop superfamily and accompanying these pentameric ligand-gated ion channels, there are nicotinic acetylcholine receptor (nACHR), zinc-activated ion channel, $GABA_A$ receptor ($GABA_AR$), and serotonin type-3 receptor (Zhu, 2022).

There are two arrangements in which a glycine receptor can be found, and it is as either αβ-heteromers or α-homomers arrangements. These two arrangements are found at different synaptic locations. The glycine receptor that are heteromers are found in postsynaptic neurons as receptors that are synaptically localised. The homomers are part of glycine release control and are located at site of the presynaptic neuron. In heteromeric glycine receptors, the β subunit of the GlyR is crucial because at the postsynaptic sites, it hosts the binding site for gephyrin, a scaffold protein, whose role of GlyR complexes stabilisation (Grudzinska et al., 2005). Furthermore, GlyRβ also have a functional role due to its contribution to the function of the glycine receptor and not just a structural role (Wiessler et al., 2024).

According to H. Yu et al. (2021), mediation of the fast inhibitory synaptic neurotransmission is carried out, solely, by heteromeric glycine receptors due to the presence of the β subunit. This subunit, through scaffolding proteins interaction, allows for clustering to occur at the synapse which facilitates synaptic transmission. This study illustrated how an unexpected stoichiometry of 4:1 is assembled by the α2 and β subunits to produce native electrophysiological properties-containing glycine receptors. H. Yu et al. (2021), also highlighted the consistency of heteromeric α2β GlyRs having a 4:1 stoichiometry and a single beta subunit provides the GlyR's electrophysiological properties, which is a characteristic property of GlyRs that are heteromeric. However, the results also showed how a GlyR is rendered non-conductive if more than one β subunit is present within one GlyR. Furthermore, linkage of GlyR to scaffolding proteins is univalent with the presence of a single β subunit and thus cluster properties are regulated solely by the scaffold.

3.3. *Glycine receptor subtypes*

The subtypes of glycine can be characterised into homomers and heteromers. A characteristic of homomeric GlyR is that it does not have a β-subunit. This specific subunit which is present in heteromeric GlyRs crucial for the clustering of the glycine receptor and also synapse stabilisation is obtained through the interaction between gephyrin, which is a scaffolding protein, and the β-subunit's intracellular domain (ICD). (San Martin et al., 2022).

In their article, San Martin et al. (2022) described α3 GlyRs contribute to hearing and control of breathing while memory recognition, cortical migration and neurogenesis are carried out with the aid of GlyR with α2 subunits. It was also noted by the authors that both α3 and α2 GlyRs have central roles in alcohol addiction and autism along with other neurological diseases. Subcellular function and localisation are adjusted when modifications of a post-translational nature modify β GlyR. This links β-subunit modification to the phenomenon of plasticity that is pain-related which is related with glycinergic transmission. Glycine receptors with α1 have a contribution to physiological functions that are described as essential, and they are largely expressed in the brainstem and spinal cord. The expression of α2GlyRs in adult mammals' dorsal horn is very minute and even absent (San Martin et al., 2022).

In their paper Scott et al. (2015), mutations in the M1 domain (α1Q−26′E) led to a decreased channel conductance in hetero- and

homomeric receptors and increased active period, whilst the same mutations in the β subunit has caused such subunit to be static, relatively, during GlyR activation. The results also show that differing mutations in α1 subunit may lead to stronger activation or even disrupted activation. This authors Scott et al., (2015) imply that the coupling-energy change between residues that are spatially clustered at different positions in the M2-3 linker and M2 domains are crucial, for the GlyR activation and well as the activation of other pentametric ligand-gated ion channels.

From this review article, San Martin et al. (2022), concluded that based on current experimental results, chronic inflammatory pain is triggered by glycinergic dis-inhibition of the spinal cord, a process that involves synaptic α3β and α1β GlyRs phosphorylation. Though authors also state that the roles of β and α2 remain unknown, GlyRs along with the glycinergic system's other proteins have a highly dynamic placidity due to the diversity of molecular mechanism.

Zeilhofer et al. (2021) in their article state that the superficial layer of the spinal dorsal horn is enriched to a high degree with α3GlyRs. This site is crucial for nociceptive system processing. Zeilhofer et al. (2021) illustrate a diagram of a glycinergic synapse where the released glycine neurotransmitter would bind to the α/β heteromeric GlyRs that are found on the postsynaptic terminal where it would be anchored by gephyrin, a scaffolding protein. It is the glycine release that riggers an inhibitory potential on the postsynaptic terminal. GlyRs are also present on the presynaptic site. The presynaptic GlyR is a homomeric receptor and their activation was suggested by the authors to cause an enhanced release of the glycine transmitter.

In Fig. 2, the diagram illustrated is based on the paper by Zeilhofer et al. (2021) and it depicts a glycinergic synapse where the released glycine neurotransmitter would bind to the α/β heteromeric GlyRs that are found on the postsynaptic terminal where it would be anchored by gephyrin, a scaffolding protein. It is the glycine release that riggers an inhibitory potential on the postsynaptic terminal. GlyRs are also present on the presynaptic site and the presynaptic GlyR is a homomeric receptor. Their activation was suggested by the authors to cause an

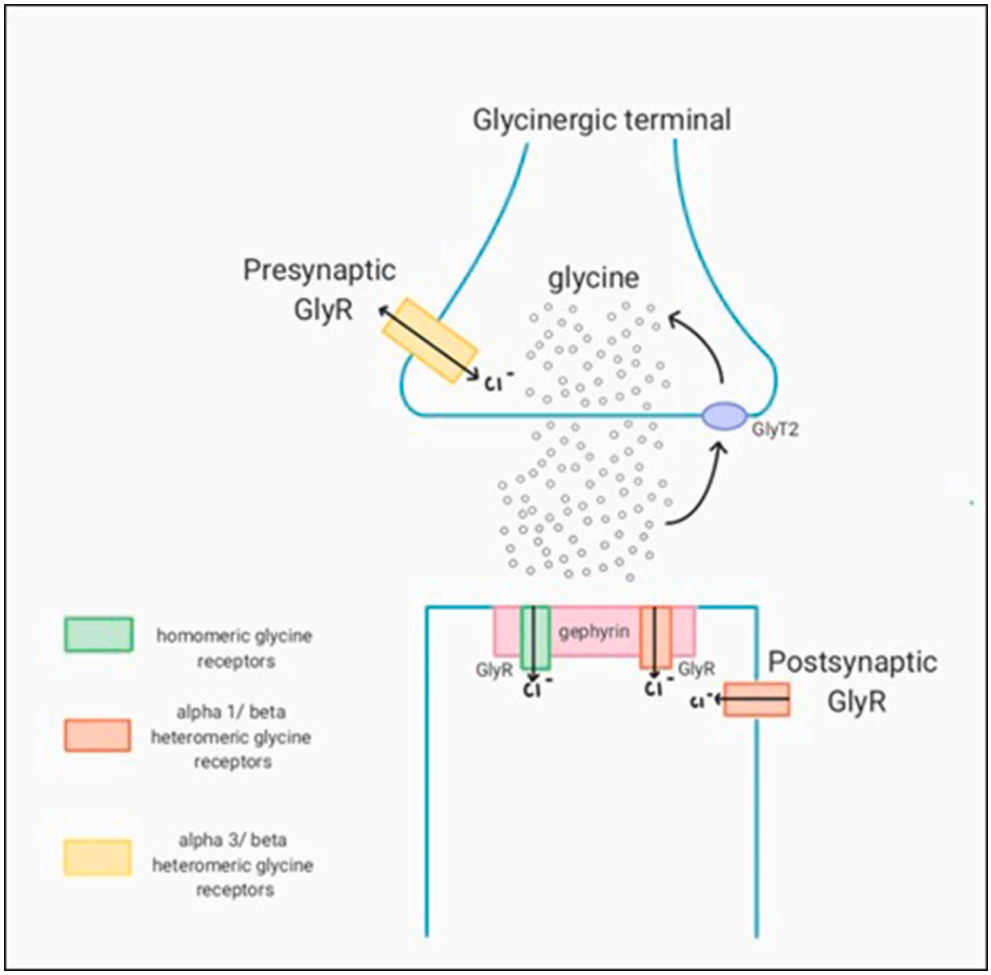

Fig. 2. The Glycinergic synapse illustrating the release of glycine from the presynaptic terminal, the reuptake of glycine by a glycine transporter 2 (GlyT2). Distribution of the different subtypes of GlyRs found on the presynaptic and postsynaptic terminals of the neuron. Scaffold protein gephyrin anchoring the postsynaptic α/β heteromeric receptors. Diagram adapted from Zeilhofer et al. (2021).

enhanced release of the glycine transmitter.

In a recent study conducted on pig brainstem and spinal cord, Zhu and Gouaux (2021), state that native GlyRs structures, when studied by cryo-electron microscopy (Cryo-EM), have a predominant 4α:1β stoichiometry of the subunit of heteromeric receptors. The results also revealed certain insight regarding heteromeric receptor structures. A phenylalanine was a unique residue was found in the pore of the β-subunit and the picrotoxin site, which is described as canonical, was disrupted by this residue. It was suggested that this disruption by residue is the reason why the β-subunit causes alteration on the pharmacology of the ion channel since the subunit's inclusion would break the symmetry of the receptor. Furthermore, a distinct structural difference adopted by the α(+)–β(−) and α(+)–α(−) interfaces when compared to the β(+)–α(−) interface. Zhu and Gouaux (2021), also noted some receptor complexes that were incomplete as shown by α-tetramers and α-trimers whose partially assembled architecture.

3.4. Synaptic transmission action mechanism

The channel of the glycine receptor is opened when the glycine amino acid binds to the receptor. The ion channel is formed M2 helices of each GlyR subunit and when it is opened by glycine, its agonist, there is an influx of negatively charged chloride ions into the cell for a short-term period. Due to the influx of negative ions, there would be a temporary increase of chloride ion concentration in the cell which leads to membrane hyperpolarisation. This would prevent easy excitation of the cell and provide an overall inhibitory effect (Aguayo-Cerón et al., 2023).

In their study, J. Yu et al. (2021), commented on how signal transduction in pLGICs is mediated at chemical synapses and how when a neurotransmitter binds to a pLGIC, there is transition between different states such as when the channel at rest, when it is open or desensitised. The authors also noted how full agonists neurotransmitters cause the channel to open as much as it could to produce the maximum yield probabilities while neurotransmitters that are partial agonists have a lower maximum yield. Prior to the study, the authors noted that the activation of the ion channel in a glycine receptor is not a simple mechanism where there is isomerisation form a resting state to an open state. Instead, there is an involvement of one or more intermediates in the pre-open state of the channel (Lape et al., 2012). It was also noted, as general feature in pLGICs, the closed states of the channels have multiple agonists bound to it and there is also an increased agonist affinity in close intermediate states.

By using the technique of electrophysiology, J. Yu et al. (2021) studied how glycine acts as a full agonist for the GlyR with 97% maximum Po and how γ-amino butyric acid (GABA) and taurine are partial agonists to GlyR. The results illustrated how channels in a closed and agonist bound are populated by partial agonists. In terms of the binding side for the neurotransmitter in glycine complexes, the carboxyl and amino groups of the agonists are able to form multiple interaction of hydrogen bonds and a cation-π contact. GlyR with glycine bound to it was found to populate both close and open states. For the partial agonists the Po is around 39% ± 3% and for GABA it is around 66% ± 3%. Furthermore, for both GABA and taurine the results illustrated a difference between receptor residue and agonist's amino group interaction. The data from this study illustrated how in an open state of a GlyR and other pLGICs, partial and full agonists complexes are not identical. The binding site of full agonist, such as glycine, is more compact when compared to partial agonists and this is correlated with the efficacy of the agonist type. The partial agonists such as taurine, also illustrated to produce conformational changes in the ECD and ECD-TMD units within the GlyR, in order to transition between states.

In the study J. Yu et al. (2021) also shows that GlyR in a resting/apo state would undergo a contraction of the binding pocket where the agonist would attach to the receptor. The contraction would cause loop C found on the ECD of the GlyR to shift from an uncapped to a capped configuration which in turn would lead to loop B of the ECD to move close to the agonist. The binding pocket contraction extent is dependent on agonist type whereupon glycine agonist would have the smallest volume-having binding pocket. Furthermore, changes occur to the ion channel pore conformation during the GlyR gating mechanism. When transitioning from a closed to an open state, a rotation of approximately 8.6° in a clockwise manner occurs at the TMD of each of the GlyR subunit, mostly at the M2 helix of TMD. This would allow the pore to expand and thus the ion channel would open cause Cl^- to permeate through to the cell. When the GlyR transitions from an open to a desensitised state, it is the TMD that undergoes the most conformational changes, with the largest inward motion occur by the M2 helix of the TMD.

It is the ECD that promotes the transitions of GlyR to shift from a closed into an open states and the study also illustrated how when there is sustained partial agonist biding would cause the promotion of further transition into the desensitised state. This is seen in Fig. 3 which illustrated based on the findings from the paper by J. Yu et al. (2021).

According to Shi et al. (2023), their study, using voltage-clamp fluorometry, reported a conformational change occur prior to the opening of the ion channel pore of the GlyR, which is elicited by glycine. The

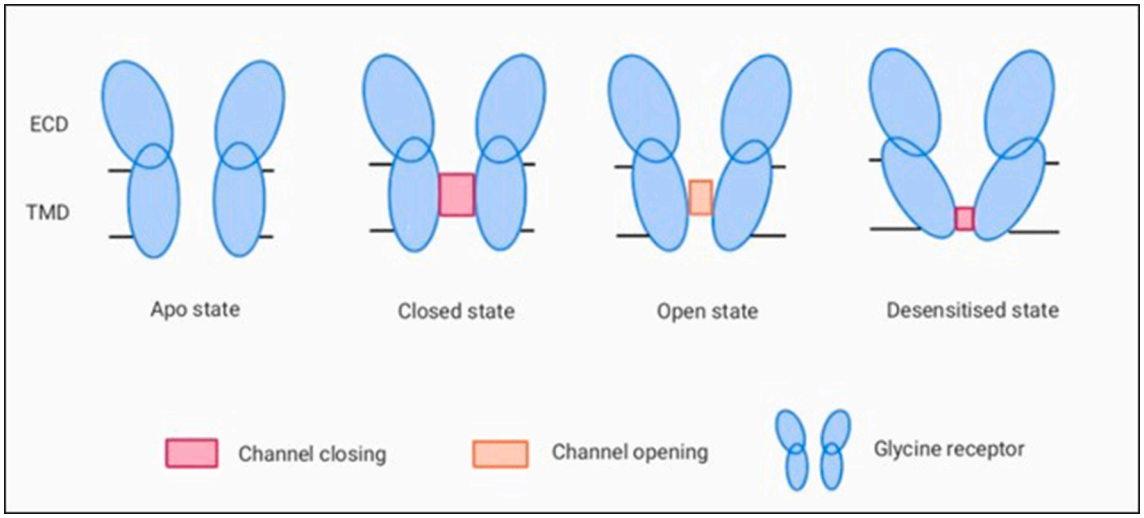

Fig. 3. Glycine Receptor In different states during glycine receptor gating mechanism Illustration adapted from J. Yu et al. (2021).

Table 2
Summary table containing the important points about the glycine, GlyR structure, subtypes of GlyRs and the synaptic mechanism of GlyRs.

Glycine	• Non-essential, simplest amino acid (acetic acid) (Aguayo-Cerón et al., 2023) • Generated in kidney and liver (Imenshahidi and Hossenzadeh, 2022) • Endogenously synthesized in body (Imenshahidi and Hossenzadeh, 2022) • Causes hyperpolarisation through influx of chloride ions through GlyRs (Shahsavar et al., 2021) • Positive modulator of GlyRs (Shahsavar et al., 2021) • Positive modulation, excitation of neurons and plasticity in glutaminergic synapses (Shahsavar et al., 2021) • Roles: collagen and purine production, tissue restoration, improvement of muscle tone, anti-inflammatory, protein-configuration, transmission of pain, gene regulation expression, modulates growth hormone and delay muscle degeneration (Aguayo-Cerón et al., 2023) • Homeostasis of glycine maintained by GlyT1 and GlyT2 (Shahsavar et al., 2021)
Structure of GlyRs	• Pentameric ligand-gated chloride channel (Zhu, 2022) • Composed of β-subunit and 4 α-subunits, TMI-4, large ECD and short extra-cellular C terminus (Wiessler et al., 2024) • Part of Cys-loop superfamily (Zhu, 2022)
GlyRs subtypes	• Either αβ-heteromers or α-homomers arrangements (San Martin et al., 2022) • Heteromeric GlyRs in postsynaptic neurons in 4α:1β stoichiometry (Zhu and Gouaux, 2021) • Homomeric GlyRs in presynaptic neurons (Zeilhofer et al., 2021) • β-subunit crucial for clustering of heteromeric GlyRs and interacts with gephyrin to stabilise synapse (San Martin et al., 2022) • α1 found in brainstem and spinal cord and is crucial for essential physiological functions (San Martin et al., 2022) • α2 subunit crucial for neurogenesis, memory recognition and cortical migration (San Martin et al., 2022) • α3 subunit aid in breathing control and hearing (San Martin et al., 2022) • α3GlyRs enriched in spinal dorsal horn crucial for nociceptive system processing (Zeilhofer et al., 2021)
GlyRs synaptic mechanism	• Glycine binds to GlyR and initiates hyperpolarisation through chloride ion influx (Aguayo-Cerón et al., 2023) • GlyRs transitions between open, desensitised, and closed states through binding kinetics and allosteric modulation (agonist and antagonists) (J. Yu et al., 2021; Shi et al., 2023; Gibbs et al., 2023)

gating mechanism of GlyR was investigated using fluorometry at the extracellular-transmembrane. The GlyR channel was weakly activated when low concentrations of partial agonists, mixtures of strychnine and glycine, as well as glycine on its own, were exposed to it, even though these concentrations still triggered a signal of full fluorescence. The results of Cryo-EM, also show a the highly dynamic nature of partial agonist-bound GlyRs which marks a level of structural flexibility at both the orthosteric site of the GlyR and the extracellular-transmembrane. Thus, this study highlights plasticity of the structure within the allosteric effectors' mechanism occurring on the glycine receptor.

A study was carried out by Gibbs et al. (2023) on α1βBGlyRs of zebrafish, where the receptors were exposed to various agonist types such as the agonist glycine, glycine/ivermectin which is a combination of an agonist and a positive allosteric modulator, or strychnine which is an antagonist. Cryo-EM structures that results from this illustrated that a distinctly different pore conformation for each structure along with various symmetry degrees. In the desensitised state, glycine/ivermectin and glycine were noted while strychnine was shown in the closed GlyR state. It was also noted that ivermectin, binds in a pose that is distinct at the interface between β-α however it also binds to the all the five interfaces. No fiduciary marker was needed in order to identify structures as they were identified based solely on the specific features of each subunit. These features also confirmed the 4α:1β stoichiometry GlyR subunit conformity that was observed in recent years.

A summarised table containing the important points about the glycine, GlyR structure, subtypes of GlyRs and the synaptic mechanism of GlyRs is shown in Table 2.

4. Modulation and regulation of glycine receptors

4.1. Factors that affect glycine receptor activity

4.1.1. Gephyrin

There are several factors that would bring about a change to GlyR activity. Gephyrin is a very crucial because it a scaffold protein which anchors GlyRs on the postsynaptic neuron. The gephyrin itself binds to the GlyR by attaching to the tubulin and β-subunit of the receptor (Betz, 1990). This attachment results in the clustering of GlyRs together on the postsynaptic neuron (San Martin et al., 2022). In a study done by Chapdelaine et al. (2021) it was stated the presence of postsynaptic scaffold proteins, such as gephyrin, on postsynaptic neurons is to ensure synaptic transmission that is efficient. This efficient is due to their site where the position in a synapse would cause GlyR immobilisation, ready to receive the neurotransmitter glycine when released from the vesicles at their release sites on the presynaptic neurons. Gephyrin is described in this study as the scaffold protein that is chiefly responsible, in inhibitory synapses, for assembling clusters that are dense in number in order to provide ample sites for GlyRs to bind to them. Due to their ability to bind to β subunit of the glycine receptor, it is the heteromeric receptors that can bind to gephyrin.

In their study Chapdelaine et al. (2021) also note how there is the formation of complexes composed of receptor and scaffold proteins that occur outside of the synapses facilitating GlyRs interaction extra-synaptically. Through fluorescence imaging of recombinant Dendra2-gephyrin, kinetics exchange was observed, and the authors observed how there was no indication of primary dependence of gephyrin molecules number, at synapses, on the complexes of GlyR-gephyrin exchange. The results from this study show how the domain, illustrating the interaction between the receptor and the scaffold domain, hosts a tight interaction. However, there is some loose interactions between scaffold and receptors extrasynaptically. The results also demonstrate that at inhibitory synapses, the stabilisations of gephyrin and GlyRs that are reciprocal to each other.

Clusters of heteromeric GlyRs and gephyrin can be produced through the trimerization of the domains of the gephyrin scaffold protein which then dimerises to GlyR hence producing such clusters (H. Yu et al., 2021). The E domain of the gephyrin attaches to the β-subunit of GlyRs and how the pore on the β subunit is partially restricted causing a lack of conductive electro physical properties of GlyR when multiple β-subunits are present in each GlyR. The study conducted by H. Yu et al. (2021) also demonstrated how the cluster properties are regulated by the scaffold and it is the β-subunit that ensures linkage of GlyR-scaffold that is univalent.

4.1.2. Strychnine

An antagonist of GlyR is the alkaloid strychnine which has the ability to bind to GlyRs at the same binding pocket site that glycine would bind to the glycine receptor (Graham et al., 1985). In their study (H. Yu et al., 2021), described GlyRs as being sensitive to strychnine. Strychnine is described by Shi et al. (2023), as a competitive as opposed to glycine, which is a full agonist of GlyR. In this study, by exposing GlyR solely to strychnine, this antagonist shifting the spontaneous equilibrium of the GlyR back to the resting state, from the intermediate conformation. The ECD, when in is in the closed-channel state (tau-closed), is dynamic and the orthosteric site open spontaneously causing an increase in strychnine binding compatibility. The data from the study also suggests that when there is a mixture of agonists such as glycine and strychnine, the GlyR will overall retain conformation in an intermediate-like state. There were also some sites which were observed to bind to strychnine while in an expanded state that is resting (Shi et al., 2023). Huang et al.

(2015), in their review, note how strychnine when bound to the GlyR there is the presence of M2 helices that are parallel to each other where the channel axis is pointed at by 9′L of the helices. The pathway through which Cl^- permeates (permeation pathway) is blocked by this arrangement of the M2 helices due to a resulting diameter of the channel to be 3 Å. For human GlyRs that are α2-β heteromeric and strychnine-bound, there are two obtained states. There is a constriction at the helices' 9′L for both states even though there is a difference in the two states' TMD conformation. Strychnine has been utilised in experiments of affinity purification and binding of radioligands (Zhu, 2022).

4.1.3. Ivermectin

Ivermectin is a derivative of avermectin, which acts antiparasitic drug used to treat parasitic infections in both animals and humans (Johnson-Arbor, 2022). However, it also acts as GlyR potentiator which has the ability to enhance the sensitivity of glycine to the glycine receptor and increase the possibility of opening of the channel (Popen) (Zhu, 2022). Several homomeric glycine receptor were discovered for their ability to be bound to ivermectin at M1 and M3 interface in order to form an interaction of a polar nature with M2 of the TMD. When compared to when glycine binds to the GlyR, ivermectin will cause a contraction of the intracellular ion channel opening causing more chloride ions to permeate through the channel (Zhu, 2022). This potentiator is found distinctly bound at the interface between β and α, even though ivermectin can bind to all five of interfaces and it is described as a positive allosteric modulator of the glycine agonist (Gibbs et al., 2023).

4.1.4. Picrotoxin

This chemical is a convulsant drug used for research studies as it has the ability to be an active stimulant of the nervous system (Bukanova et al., 2024). A channel blocker of glycine receptor is picrotoxin which acts to inhibit the permeation of chloride ions through the GlyR channel. The pores of the Cys-loop receptors such as GlyRs are blocked by picrotoxin and this causes there to be discrimination between heteromeric and homomeric GlyRs (Zhu and Gouaux, 2021). Heteromeric GlyRs are less sensitive to the effects of the picrotoxin channel blocker when compared to homomeric GlyRs (Zhu, 2022). The decreased sensitivity of heteromeric GlyRs are due to these receptor types exhibiting resistance picrotoxin block. Furthermore, the presence of the bulky sidechain consisting of β-subunit leads to steric hindrance and hence picrotoxin is blocked from the site where binding can occur (Zhu and Gouaux, 2021).

4.2. Endogenous modulators

There is an array of ligands that act as endogenous modulators and these can be categorised as partial agonists such as GABA, taurine and β-alanine or full agonists such as glycine itself. GlyR activation is brought about by binding of agonists that in turn result in the flow of chloride ion (Cl^-) across the membrane. This Cl^- equilibrium potential regulates the chloride ion flow and hyperpolarisation of the membrane is induced and thus neuronal activity is inhibited (Zhu, 2022).

Allosteric modulation of GlyRs is also regulated by various endogenous modulators or synthetic compounds which fit into allosteric modulation sites. Even though this modulation resulted in the discovery of these allosteric binding sites, it is unlikely that some of these compounds are used in a therapeutic manner. However, they are important for programs pertaining to drug discovery. Zinc can act as a bidirectional modulator of GlyR activity where concentrations that are considered as micromolar (20–50 μM) lead to GlyR inhibition while concentrations that are sub-micromolar (20nM–1μM) would cause potentiation of GlyRs. Zinc has been noted for its ability to modulate neurotransmission in the CNS, in a unique manner (Zeilhofer et al., 2021). In their research Zhang et al. (2016) concluded how in glycinergic synapses that are artificial, the zinc ion (Zn^{2+}) has a high chance to be released phasically and increase to at least 1 μM synaptically when there is a single presynaptic stimulation.

4.2.1. Tropeines

There are also certain drugs that affect glycine receptors, and two examples are tropeines and zonisamide. Tropeines are drugs that are used as antiemetics, which act as receptor antagonists. Specifically, it is two tropeines; tropisetron and MDL-72222 that, at concentrations of nanomolar proportions, could also cause potentiation of the activity of GlyRs. It is these two tropeines that bind to the extracellular domain of the GlyR through either an interface between one β and one α subunit or an interface between two α subunits. The main glycine receptor subtypes that were researched for their effect as tropeines are α1 GlyRs and α3 GlyRs, the latter to a lesser extent. Tropisetron has also exhibited α2 GlyRs inhibition (Zeilhofer et al., 2021).

4.2.2. Zonisamide and sulfonamides

Zonisamide is drug used for its antiepileptic properties and it has been shown to facilitate native and recombinant α1- α3 GlyRs subtypes' activation at concentrations of a therapeutic calibre (Zeilhofer et al., 2021)). In their study Devenish et al. (2021) explore the anticonvulsant effects of zonisamide on human GlyRs that are homo-oligomeric and recombinant. When this drug was compared to tiagabine and ganaxolone, which are also anticonvulsants and GlyRs modulators, zonisamide resulted to be the most efficacious of the three as exhibited by the highest EC_{50} value for α1- α3 subtypes. The results also illustrated that this drug is a non-selective positive modulator of GlyRs. In the medial/lateral entorhinal cortex, currents that were heteromeric and

Table 3

Factors effecting GlyR activity	• Gephyrin – anchor scaffold protein, influences stabilisation and clustering (San Martin et al., 2022, p. 848642), (Chapdelaine et al., 2021), (J. Yu et al., 2021) • Strychnine – antagonist (Zhu, 2022), (H. Yu et al., 2021; Shi et al., 2023) • Ivermectin – potentiator and glycine sensitivity enhancer (Johnson-Arbor, 2022; Zhu, 2022; Gibbs et al., 2023) • Picrotoxin – channel blocker
Endogenous Modulators of GlyRs	• Partial agonists – taurine, GABA and β-alanine (Zhu, 2022) • Full agonist – glycine (Zhu, 2022) • Zinc – bidirectional modulator (Zeilhofer et al., 2021) • Tropeines – antagonists used as antiemetics (Zeilhofer et al., 2021) • Zonisamide – non-selective PAM, antiepileptic drug (Zeilhofer et al., 2021; Devenish et al., 2021) • Sulfonamide – potentiator and PAM, antibiotic properties (Gallagher et al., 2022) • Endocannabinoids – inhibitor, inactivators and potentiator with anti-psychotic, anti-nociceptive, anti-convulsant, anti-emetic and antioxidant effects (Schmiedhofer et al., 2022; Gallagher et al., 2022; Oz et al., 2022; Zeilhofer et al., 2021; Schmiedhofer et al., 2022) • GlyT1 and GlyT2 - maintain homeostasis of glycine uptake (Salceda, 2022; Shahsavar et al., 2021; San Martin et al., 2022) • Ethanol – different allosteric modulation in GlyR heteromers and homomers (Muñoz et al., 2021)
Pharmacological Modulation	• Zonisamide - potentiates GlyRs and used in temporal lobe epilepsy treatment (Devenish et al., 2021) • CBD and THC - restore GlyR function in cocaine-induced seizures (Oz et al., 2022) • Colchicine, pregnenolone sulphate and torpiseteron – a non-selective GlyR antagonists (McEwan and Robinson, 2021; Wei et al., 2021; Zhang et al., 2024; Alexander et al., 2021) • Ethanol, alcohols, intravenous anaesthetics – GlyRs potentiators (Alexander et al., 2021)

homomeric glycine-mediated, were potentiated by 100 μM zonisamide, suggesting that the anticonvulsant properties of zonisamide is mediated by GlyRs (Devenish et al., 2021).

Sulfonamides (SO_2NH_2) are antibiotics that are bacteriostatic which are used for allergy and bacterial infections. Furthermore, sulfonamides are therapeutically used for hypertension, glaucoma and epilepsy. 4-Fluoro-N-(2-(quinolin-8-yloxy)ethyl) benzenesulfonamide was able to potentiate both α3GlyR and α1GlyR and it was described to be the most efficacious in terms of sulfonamides. The hypothesis behind the positive agonistic properties of sulfonamides is towards receptors such as glycine receptors is sulfonamides' ability to stabilise the GlyR's orthosteric pocket where binding occurs. Zonisamide is an example of a sulfonamide moiety and so it acts as a positive allosteric modulator (PAM) of GlyRs. Pharmacologically, the development of GlyRs' PAMs has been solubility- and metabolism-centred in order to ensure that use of sulfonamide types as drugs which are availably orally (Gallagher et al., 2022).

4.2.3. Endocannabinoids

These endogenous modulators of GlyR are neurotransmitters function as tissues hormones with multiple targets and they are endogenous derivatives of lipid molecules (Schmiedhofer et al., 2022). Cannabinoid receptors 1 and 2 (CB1 and CB2) are combined with exogenous ligands which are called endocannabinoids and two examples of endocannabinoids, which are pivotal activators are 2-arachidonoyl glycerol (2-AG) and N-arachidonoylethanolamine (AEA) (Gallagher et al., 2022). CB receptors and endocannabinoids are part of the cannabinoid system and they are involved in anti-nociceptive, anti-emetic, anti-convulsant, anti-oxidant and anti-psychotic effects that are illustrated by cannabinoids (Oz et al., 2022).

Predominantly, these endocannabinoids are found to inhibit modestly or inactive both α3GlyR and α2GlyRs but potentiate α2GlyRs. This ability of endocannabinoids to bind to GlyR is due to them being highly homologous with both CB receptors in terms of the sites of cannabinoids' predicted interaction. That being said, the bind sites on the GlyR is determined by the polarity of the endocannabinoid head as the different endocannabinoids are prone to be affected by an array of mutations found on the ICD, ECD and TM2 of the GlyR, due to varying polarity. This indicates that various regions of the GlyR are involved and endocannabinoids have a complex modulatory effects (Gallagher et al., 2022).

These eicosanoids, which are lipophilic lipid signalling molecules, activate CB_1 and CB_2. AEA and other neutral compounds are known to potentiate α1-α3 GlyRs however, conjugates of arachidonoyl cause potentiation in the function of GlyR and has shown various effects upon subtypes of GlyR (Zeilhofer et al., 2021). At uppermost TMD of the α1-GlyR there have also been suggested, additional sites for cannabinoids interface. There is an overlap of sites for cannabinoids in the TMD because they can also be used by molecules that are lipophilic such as cholesterol. The sites available for the interaction between GlyR and either lipid molecules or cannabinoids, are called lipid-associated binding sites and they are described as grooves found along the lipid collar within the TMD (Schmiedhofer et al., 2022).

4.2.4. Glycine transporters

Gly1 and Gly2 are plasma membrane transporters that are endogenous modulators of GlyR because it is through their ability for glycine reuptake into the cell from the synaptic cleft (Salceda, 2022, p. 947563). These protein transporters are key in the glycinergic system through their chloride- and sodium-dependent reuptake ability of the neurotransmitter (Salceda, 2022).

Glial cells are predominantly populated with GlyT1 (Salceda, 2022), while ample GlyT2s are found within the brain stem and the spinal cord (San Martin et al., 2022). According to Shahsavar et al. (2021), GlyT1 is able to regulate the inhibition or excitation of glycine neurotransmitter. This would in turn endogenously modulate GlyRs since any inhibition to the GlyT1 would cause neurotransmitter signalling prolongation since less glycine is re-uptaken causing slower GlyRs hyperpolarisation and Cl^- permeation in the post-synaptic neuron. Pharmacological inhibition of the GlyT1 can be carried out for therapeutic study for a vast range of CNS disorder such as cognitive impairment and schizophrenia.

GlyT2 distribution corresponds to the prominence of glycinergic inhibitory post-synaptic currents (Gly-IPSCs), that are detectable. The ample expression of subunits of β and α1 in GlyRs in the spinal cord as GlyT2 supports the detectable Gly-IPSCs (San Martin et al., 2022).

4.2.5. Ethanol

The ability of GlyR, when activated, to decrease the excitability of neurons, in the areas associated with motor control, functions of respiration and sensory information, is altered significantly when the body is intoxicated with ethanol (Muñoz et al., 2021). In heteromeric α2β GlyRs, ethanol was found to have a different allosteric modulation than when homomeric α2 GlyRs interact with ethanol, and this is due to a novel way of how the β-subunit affect the sensitivity of α2 subunits to ethanol. In their study, Muñoz et al. (2021), found that there is a substantial potentiation of heteromeric α2β GlyRs by ethanol, zinc ions, propofol and trichloroethanol, while homomeric α2 is insensitive. Ethanol sensitivity was blocked when GlyRs containing α2 and β-subunit are mutated, however propofol still cause potentiation. Thus, there is a selective mechanism shown for heteromeric and homomeric α2 GlyRs when low concentrations of ethanol are used. This suggests pharmacological potential in areas of abundant α2 GlyR expression in the brain (Muñoz et al., 2021).

Muñoz et al. (2021), illustrate the different allosteric sites at which positive modulators of GlyRs. Tropeines and sulfonamides bind between adjacent complementary and primary subunits at the ECD. Cannabinoids, avermectins, anaesthetics, alcohols, lipids and neurosteroids are found within the TMD of the GlyR.

4.3. Pharmacological modulation

In their review, Gallagher et al. (2022), effects of an antinociceptive nature are shown when GlyRs undergo positive modulation which may have nociceptive signalling influences and have novel therapeutic potential for pain management.

Temporal lobe epilepsy is linked to GlyRs and so modulatory anticonvulsants such as zonisamide, which has resulted to have the highest efficacy out of 23 other anticonvulsants for various subtypes of GlyRs. Whilst zonisamides are used for epilepsy, trial have been carried out where zonisamide is used to treat neuropathic pain such and other neurological conditions. Novel drugs able to be developed for alleviation of neuropathic pain by targeting subtypes of GlyRs that have α3 subunits and zonisamide's analgesic effects may possibly involve such mechanism. AM-1488, a non-selective modulator of GlyR, which arises from a scaffold in α3 GlyRs that have similar moiety of sulfonamide with zonisamide, was found to cause reduction in allodynia in mice with pain that is neuropathic. Hence AM-1488 was described as having parameters of pharmacokinetics that are favourable (Devenish et al., 2021).

CBD and THC and other cannabinoids were found to restore dysfunction in GlyRs in the brain to counteract seizures that were induce by cocaine use and this occurs through the use of the cannabinoid receptor interface on GlyRs. In the mice with hereditary startle-hyperekplexia due to α1 GlyR mutation, this receptor dysfunction was recused by dehydroxyl-CBD (Oz et al., 2022).

There are many drugs that cause pharmacological modulation of GlyRs. A few examples of are colchicine, an anti-inflammatory used to treat Bechet's disease, Familial Mediterranean fever, and gout (McEwan and Robinson, 2021, pp. 101–12), pregnenolone sulphate, which is a neurosteroid (Wei et al., 2021, pp. 672–9) and torpiseteron, which is used to treat vomiting and nausea post operation (Zhang et al., 2024, pp. 1–9). These drugs act as non-selective GlyR antagonists (Alexander et al., 2021).

Table 4

Clinical Relevance of GlyRs	• Chronic and nociceptive pain (Harvey and Vandenberg, 2021, p. 1676), (El Khoueiry et al., 2022; San Martin et al., 2022; Breitinger and Breitinger, 2023; Mariqueo et al., 2023; Valdés-Jorquera et al., 2022) • Hyperekplexia and startle disease (Aboheimed et al., 2022; Dilger and Shanawaz, 2021; Zhan et al., 2021; Schaefer et al., 2023) • Autism Spectrum Disorder (Chen et al., 2022) • Epilepsy (Sanli et al., 2021) • Autoimmune disease: • Stiff person syndrome (Wiessler et al., 2024) • Anxiety and Alzheimer's (Botto et al., 2022)

General anaesthetics that intravenous, such as propofol, pentobarbitone and minaxolone, act as modulators of GlyRs while ethanol and alcohols of higher order acts as direct allosteric effectors of the glycine receptor. Furthermore, 1-1-1-trichloroethane and toluene, which are inhaled drugs of abuse may interact with the same GlyR binding sites where volatile anaesthetics and alcohols interact however, all cause GlyR potentiation (Alexander et al., 2021).

Table 3 encompasses all the main points of Chapter 3 with regards to the factors and endogenous modulators of GlyRs as well as information regarding pharmacological modulation of GlyRs.

5. Clinical relevance of glycine receptors

5.1. Chronic pain and nociception

In their study, (Harvey and Vandenberg, 2021), state how chronic pain and inflammatory treatment through glycinergic neurotransmission modulation, has been gaining popularity and how GlyT1 and GlyT2 and GlyRs are considered as crucial targets for such therapies. In this article, the authors highlight how within the dorsal horn of the spinal cord, a site that is crucial for nociceptive processing, there is a high density of α3GlyR subtype. Thus, there exists a link between this subtype and pathway signalling sensation of central inflammatory pain, which is allows the possibility of modulating such pain through targeting such α3GlyR subtype. That being said, the authors acknowledge that there is evidence of α1GlyRs as well within the spinal dorsal horn which can also be targeted selectively for inhibition of potentiation of GlyRs in order to manage pain. It was also reported that patients with mutations in the GlyT2 or α1GlyR genes which manifested in hyperekplexia/startle disease presented with a lower threshold of pain which highlights the role of glycinergic neurotransmission in pain propagation within the body. Endogenous and exogenous zinc ion modulation, where the ion would exhibit analgesic properties through GlyRs' chelation modulation was also explored. Treatment through GlyRs and GlyT1 targeting is proving to be favoured when compared other treatments, because opioid receptor pathways are not targeted by modulators of GlyT1 and GlyRs. Thus, by opting to choose this treatment, the scientific community is moving one step closer towards the opting for safe, non-addictive, yet still effective, inflammatory, and chronic pain management. This article stresses the validity of how both novel and existing analgesics classes can be used to modulates these novel targets of GlyRs and GlyT1 (Harvey and Vandenberg, 2021).

In their article, San Martin et al. (2022), state how chronic pain occurs when the inhibitory control of the glycinergic system is disrupted. The authors highlight how there is a lack of study done on the participation of β and α2 subunits and how currently, the focus remains on the role of α3 and α1 GlyRs in the disinhibition of the glycinergic system that is chronic inflammatory pain triggered. The author stress how this link between GlyRs and managing of chronic pain deems further research and has a lot of therapeutic potential.

El Khoueiry et al. (2022) in their article address how a symptom of neuropathic and inflammatory pain is mechanical allodynia which occurs when a tactile stimulus, that is normally innocuous, elicits pain. This symptom is evoked by the interaction between medullary and spinal dorsal horn which mediate tactile pain and sensation. Interneurons which are PKCγ-expressing, are crucial in pain and touch circuits, and in this study, El Khoueiry et al. (2022) around 80% of inhibitory synapses of these interneurons contain α1 GlyRs along with a GABA receptor subtype. These interneurons were found to exhibit a GlyR-only and GABAAR-only, inhibitory currents that are quantal and postsynaptic, almost exclusively and hence, possible specialisation in terms of pharmacology of these inhibitory synapses was suggested (El Khoueiry et al., 2022).

Breitinger and Breitinger (2023), suggest the potential of GlyRs as therapeutic targets in neuropathic pain that is associated with diabetes. Due to the possible contribution of GlyR to diabetic neuropathy that is induced by treatment and analgesia that is mediated by glucose, the authors suggest there is clinical relevance between the contribution of GlyR to the alteration of sensation of pain in diabetes. Hence these receptors are potential targets of therapy in novel analgesics development.

In terms of acute and chronic pain, Mariqueo et al. (2023) state how GlyRs are recognised as pain mediators in the spinal cord with special implication on the response to Interleukin-1β (IL-1β) and other proinflammatory signals. In their study, the results showed that IL-1β inhibits the chloride currents of the GlyRs and this interaction and GlyRs immune modulation has an effect on the pain perception circulation. Valdés-Jorquera et al. (2022), highlight how glycine has a cytoprotective role and how recent evidence emerged regarding the modulation of vascular cells, in the endothelium, by glycine with α2 GlyRs involved in a mechanism that protect neurovascular supply. The article also illustrates how after an injury due to stroke, α2 GlyRs expression decreases and the VEGF/pSTAT3 signalling is able to reverse α2 GlyRs inhibition through glycine. Modulation of GlyRs by IL-1β suggests an alternative way of understanding modulation of the immune system of pathological conditions', such as cerebrovascular stoke, vascular function, which the endothelial cells actively participate in. Valdés-Jorquera et al. (2022), distinguish the therapeutic potential of allosteric modulation of GlyRs and glycine in confronting injuries that occur post-ischemia.

5.2. Hyperekplexia and startle disease

The neurological disorder of hyperekplexia is considered rare and its' characteristics in newborns are startle responses that are exaggerated. Some other defining characteristics of hyperekplexia are apnea, seizures that are nonepileptic and induced by touch or noise, and hypertonia (Aboheimed et al., 2022). As stated by Dilger and Shanawaz (2021), abnormalities that lead to hyperekplexia is often brought about by mutations within the GlyRs. According to Aboheimed et al. (2022), though the link is not properly understood yet, the same mutations and gene that cause this disease, affect GlyRs. This study provides evidence of novel mutation (A455P mutation) encoding for β-subunit of GlyRs, that causes loss of function within GlyRs, due to the interaction disruption between TM4 of the β-subunit and other subunit helices. This in turn, could possibly cause the disease of hyperekplexia (Aboheimed et al., 2022). Dilger and Shanawaz (2021) in their study state how while a mutation (V280M) that cause gain of function within the GlyR, at a synaptic level, it causes loss of function which to reduction inhibition by GlyRs, hence, the presentation of hyperekplexia within the individual.

Hyperekplexia is one example of a startle syndrome, which is an umbrella term for a group of disorders that are heterogenous, which cause responses that exaggerated and abnormal, when there is startling stimulus. Other examples of startle syndromes are neuropsychiatric startle syndromes and disorder that are stimulus-induced (Zhan et al., 2021). The characteristic symptoms of startle disease, due a disturbance in the inhibition of feedback within the brainstem and spinal cord are general stiffness in muscle, startle responses, and episodes of fatal apnea

(Schaefer et al., 2023). Individuals with startle disease were reported to contain mutations in GlyT2 and GlyR. It is the postsynaptic and/or pre-synaptic GlyRs that impair startle disease inhibitory neurotransmission. Schaefer et al. (2023), stress how further studies must be carried out to better understand the GlyR receptor dynamics, at the synaptic level, when affected by disease. Piro et al. (2021) in their paper studied how the mutations A455P and Y252S exhibit differences in hippocampal neurons when GlyR-gephryin are clustered with such mutations and these lead to synapses, that are GlyRβ positive, to be significantly reduced. The authors suggest how such mutations cause structural changes in the interactions of GlyRβ- gephyrin and concluded how alterations, loss of function or gain of function in synaptic clustering of GlyR may potentially underly the pathology of startle disease in patients that have such mutations in GlyRβ.

5.3. Autism

According to Chen et al. (2022), state that in the spinal cord and the developing cortex, it is the α2GlyRs that dictate the fate of the cell, synaptogenesis, and migration of neuronal cells. Autism spectrum disorder has been associated with gene for α2GlyR that is X-linked when it undergoes microdeletions or rare missense variations. When mutated, α2GlyR there is reduced sensitivity to glycine and/or trafficking of cell-surface and protein truncation which cause a loss in receptor function. In their study's results, Chen et al. (2022), illustrate that certain missense variants found in autism spectrum disorder can cause an alteration, loss or gain in function of α2GlyR and that these mutated α2GlyR may cause changes in memory, cognition and learning due to deregulation of migration of neuronal cells and homeostasis of the cortical progenitor.

5.4. Epilepsy

Autoantibodies for GlyRs were found within epileptic patients and in their study (Sanli et al., 2021) illustrated that how patients that are positive for GlyR antibodies had a different distribution of blood immunophenotype when compared epilepsy patients that are seronegative. This suggested that there is a physiopathology that distinct within patients that have focal epilepsy whose cause is unknown and GlyR antibody positive. This also poses a possible participation of adaptive immunity in focal epilepsy subgroups. The authors conclude how further study is required on the link between antibodies that are anti-neuronal and patients with focal epilepsy. Wu et al. (2023) in their study conclude that the bioactive constituent of Schisandra chinensis (Turcz.) Baill plant termed Schisandrin B is natural GlyR positive allosteric modulator and hence it can potentially an alternative epileptic therapy.

5.5. Autoimmune diseases

According to Wiessler et al. (2024), an example of a rare CNS autoimmune disease is stiff person syndrome (SPS) which is characterised by different phobia forms, spasming and stress of muscles and exaggerated startling to stimuli. Progressive encephalitis with rigidity and myoclonus (PERM) is also associated with SPS and together they are considered as rare disorders. SPS and PERM are associated with autoantibodies of GlyR and results from the study done by Rauschenberger et al. (2023) have indicated that autoantibodies that bind to GlyRs is not dependent on the state of glycosylation of the receptor. Hence domains of non--glycosylated receptor that are purified, that harbour autoantibody epitope, can additionally provide an experimental marker tool to detect the presence of autoantibodies in the blood serum of patient. In their study, Wiessler et al. (2024) provide evidence for the use of GlyRβ as a new specific autoantibody target in PERM or SPS patients because the efficacy of the GlyR would be impaired instead of affecting receptor localisation.

The higher expression and function of GlyRs that are sensitive to strychnine were found to be possibly associated with higher levels of anxiety. Such high anxiety is found in Alzheimer's disease due to atrophy with brain area such as inferior parietal lobe and right praecuneus. Such anxiety can also be due to a lower resting metabolism, Botto et al. (2022) The high expression of GlyRs in higher anxiety, which is shown in Alzheimer's, may merit further study on a therapeutic management that targets GlyRs to possibly reduce anxiety in Alzheimer's patients.

Table 4 is illustrating the main neurological disorders that are associated with GlyRs, hence indicating the receptor's clinical relevance is shown in Table 4.

6. Conclusion

Effective communication within the body, specifically in the brain, is spearheaded by the synapses and neurons, with the presence of glycine receptors being crucial as they provide fast and inhibitory neurotransmission.

The glycine receptor is widely expressed within both the central nervous system, particularly the spinal cord and the brain stem, and the peripheral nervous system. Such receptors were also found in amacrine cells on mice retina and even the renal cortex and medulla of the kidney. During embryonic development, GlyRs have been reported to have a wider network spread throughout more brain regions whereas in adulthood, these receptors are more concentrated in certain areas, namely the spinal cord. During early development, GlyRs are important as they expressed in dorsal progenitor cells and migratory neurons. The distribution of the GlyRs is correlated with and specifically tailored for the specific function of the area the receptor is found as evident in higher GlyRs expression the ventral horn of the spinal cord when compared to the dorsal horn. On the subpopulation of amacrine cell in retina of mice, a mixed synapse of GlyRs and GABA was reported, and GABA and glycine are co-released, which enhances the inhibitory signalling mechanism. They are gender differences in expression of α3 GlyRs subtype in mice and renal blood flow is influence by glycine receptor expression as well.

Glycine a non-essential amino acid produced mainly in the liver and kidney. This neurotransmitter, when released, is what induces hyperpolarisation in the GlyRs, when it binds to the receptor, it allows chloride ions to pass through the now open GlyR. It is also vita for other functions within the body such as collagen production, restoration of tissues, muscle tone improvement, anti-inflammatory and pain transmission. The GlyR is part of the Cys-loop superfamily of receptors, and it is a ligand-gated chloride channel that is in a pentameric formation. The ligand is composed of different combinations of β-subunit and 4 α-subunits to form either heteromeric GlyRs or homomeric GlyRs subtypes. All the different subunits serve for different function in the glycinergic synapse. The clustering of heteromeric GlyRs and synapse stability is brought about by the interaction between the β-subunit and gephyrin. The α-subunits have crucial role in various important physiological functions such as control of breathing, memory recognition, processing of nociceptive system and neurogenesis, to name a few. GlyRs are also composed of a four-helix TMD, and ECD and an extra-cellular C terminus. The gating mechanism of GlyR transitions between different states of closed, open and desensitised and it is influenced by the kinetics of binding and the agonist type that modulates GlyRs. Insights to conformation of pore, 4α:1β GlyR stoichiometry and allosteric modulation by antagonist and agonists are revealed by Cryo-EM studies.

Regulation and function of GlyRs are influenced by various factors and endogenous modulators. There are many important factors that have an impact on GlyR activity such as gephyrin, which allows receptor clustering and provides synapse stabilisation. Studies show that certain GlyRs are sensitive to strychnine as it acts as an antagonist while ivermectin has been reported to potentiate GlyR and enhance the receptor's sensitivity to glycine. On the other hand, picrotoxin acts as a channel blocker thus prevents chloride permeation and decrease inhibitory neurotransmission. GlyRs are also affect by various endogenous

modulators which act upon the receptor in one way or another and influence their activity. While glycine acts as a full agonist to GlyRs, β-alanine, taurine and GABA partially agonise the receptor. Bidirectional modulator such as zinc are also endogenous modulators. Other modulators which can be used as pharmacological agents such as the antagonists tropeines, sulfonamide potentiators and zonisamide non-selective positive allosteric modulators, used for epilepsy treatment, as well as endocannabinoids, ethanol, and anaesthetics for pain management.

GlyRs are linked to various neurological disorders and currently a lot of research is focused on the development of therapies that target specific glycine receptors subtypes and subunits in order to treat specific disorders. The relationship between α3 and α1 GlyRs and chronic pain and nociception is very promising and mutations in such receptors were found have an affect on thresholds of pain. Another important set of disorders that are a result of GlyR function disruption is startle disorders, namely hyperekplexia. When GlyRs undergo certain loss of function mutations in α2GlyR, there have been reports of association with development of autism spectrum disorder. Zonisamides, which are non-selective PAM of GlyRs, are used as antiepileptic drugs. However, a link between GlyR autoantibodies was found with temporal lobe epileptic patients, although further study is required. Some studies have also reported the role of glycine receptors in certain autoimmune diseases such as stiff person syndrome and high anxiety associated with Alzheimer's disease.

The constantly increasing evidence of the clinical relevance of glycine receptors in many neurological disorders, warrants further study in order to better understand and develop novel therapeutic management that target such important receptors.

CRediT authorship contribution statement

Nicole Mizzi: Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Renald Blundell:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

References

Aboheimed, G.I., AlRasheed, M.M., Almudimeegh, S., Peña-Guerra, K.A., Cardona-Londoño, K.J., Salih, M.A., et al., 2022. Clinical, Genetic, and Functional Characterization of the glycine Receptor β-subunit A455P Variant in a Family Affected by Hyperekplexia Syndrome, vol. 298, 102018. https://doi.org/10.1016/j.jbc.2022.102018.

Aguayo-Cerón, K.A., Sánchez-Muñoz, F., Gutierrez-Rojas, R.A., Acevedo-Villavicencio, L. N., Flores-Zarate, A.V., Huang, F., et al., 2023. Glycine: the Smallest Anti-inflammatory Micronutrient, vol. 24, 11236. https://doi.org/10.3390/ijms241411236.

Alexander, S.P., Mathie, A., Peters, J.A., Veale, E.L., Striessnig, J., Kelly, E., et al., 2021. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Ion Channels, vol. 178, pp. S157–S245. https://doi.org/10.1111/bph.15539.

Betz, H., 1990. Ligand-gated ion channels in the brain: The amino acid receptor superfamily. Neuron 5, 383–392. https://doi.org/10.1016/0896-6273(90)90077-s.

Botto, R., Callai, N., Cermelli, A., Causarano, L., Rainero, I., 2022. Anxiety and Depression in Alzheimer's Disease: a Systematic Review of Pathogenetic Mechanisms and Relation to Cognitive Decline, vol. 43, pp. 4107–4124. https://doi.org/10.1007/s10072-022-06068-x.

Breitinger, U., Breitinger, H.-G., 2023. Excitatory and Inhibitory Neuronal Signaling in Inflammatory and Diabetic Neuropathic Pain, vol. 29, p. 53. https://doi.org/10.1186/s10020-023-00647-0, 023-00647–0.

Bukanova, J.V., Solntseva, E.I., Skrebitsky, V.G., 2024. Factors Promoting the Release of Picrotoxin from the Trap in the GABA(A) Receptor Pore, vol. 175, 105703. https://doi.org/10.1016/j.neuint.2024.105703.

Ceder, M.M., Weman, H.M., Johansson, E., Henriksson, K., Magnusson, K.A., Roman, E., et al., 2023. The glycine Receptor Alpha 3 Subunit mRNA Expression Shows Sex-dependent Differences in the Adult Mouse Brain, vol. 24, p. 32. https://doi.org/10.1186/s12868-023-00800-9, 023-00800–9.

Chapdelaine, T., Hakim, V., Triller, A., Ranft, J., Specht, C.G., 2021. Reciprocal Stabilization of glycine Receptors and Gephyrin Scaffold Proteins at Inhibitory Synapses, vol. 120, pp. 805–817. https://doi.org/10.1016/j.bpj.2021.01.024.

Chen, X., Wilson, K.A., Schaefer, N., De Hayr, L., Windsor, M., Scalais, E., et al., 2022. Loss, Gain and Altered Function of GlyR α2 Subunit Mutations in Neurodevelopmental Disorders, vol. 15, 886729. https://doi.org/10.3389/fnmol.2022.886729.

Devenish, S.O., Winters, B.L., Anderson, L.L., Arnold, J.C., McGregor, I.S., Vaughan, C. W., et al., 2021. The Anticonvulsant Zonisamide Positively Modulates Recombinant and Native glycine Receptors at Clinically Relevant Concentrations, vol. 182, 108371. https://doi.org/10.1016/j.neuropharm.2020.108371.

Dilger, J.P., Shanawaz, M.A., 2021. When a Gain Becomes a Loss: Gain-Of-Function Glycine Receptors and Hyperekplexia, vol. 120, p. 56a. https://doi.org/10.1016/j.bpj.2020.11.573.

El Khoueiry, C., Alba-Delgado, C., Antri, M., Gutierrez-Mecinas, M., Todd, A.J., Artola, A., et al., 2022. GABAA and Glycine Receptor-Mediated Inhibitory Synaptic Transmission onto Adult Rat Lamina IIi PKCγ-Interneurons: Pharmacological but Not Anatomical Specialization, vol. 11, p. 1356. https://doi.org/10.3390/cells11081356.

Fricke, S., Harnau, M., Hetsch, F., Liu, H., Leonhard, J., Eylmann, A., et al., 2023. Cesium Activates the Neurotransmitter Receptor for glycine, vol. 16, 1018530. https://doi.org/10.3389/fnmol.2023.1018530.

Gallagher, C.I., Ha, D.A., Harvey, R.J., Vandenberg, R.J., 2022. Positive Allosteric Modulators of Glycine Receptors and Their Potential Use in Pain Therapies, vol. 74, pp. 933–961. https://doi.org/10.1124/pharmrev.122.000583.

Gibbs, E., Klemm, E., Seiferth, D., Kumar, A., Ilca, S.L., Biggin, P.C., et al., 2023. Conformational Transitions and Allosteric Modulation in a Heteromeric glycine Receptor, vol. 14, p. 1363. https://doi.org/10.1038/s41467-023-37106-7.

Graham, D., Pfeiffer, F., Simler, R., Betz, H., 1985. Purification and characterization of the glycine receptor of pig spinal cord. Biochemistry 24, 990–994. https://doi.org/10.1021/bi00325a027.

Grudzinska, J., Schemm, R., Haeger, S., Nicke, A., Schmalzing, G., Betz, H., et al., 2005. The β subunit determines the ligand binding properties of synaptic glycine receptors. Neuron 45, 727–739. https://doi.org/10.1016/j.neuron.2005.01.028.

Harvey, R.J., Vandenberg, R.J., 2021. Glycine Transporters and Receptors as Targets for Analgesics, vol. 11, p. 1676. https://doi.org/10.3390/biom11111676.

Huang, X., Chen, H., Michelsen, K., Schneider, S., Shaffer, P.L., 2015. Crystal structure of human glycine receptor-α3 bound to antagonist strychnine. Nature 526, 277–280. https://doi.org/10.1038/nature14972.

Imenshahidi, M., Hossenzadeh, H., 2022. Effects of glycine on Metabolic Syndrome Components: a Review, vol. 45, pp. 927–939. https://doi.org/10.1007/s40618-021-01720-3.

Johnson-Arbor, K., 2022. Ivermectin: a Mini-Review, vol. 60, pp. 571–575. https://doi.org/10.1080/15563650.2022.2043338.

Lape, R., Plested, A.J.R., Moroni, M., Colquhoun, D., Sivilotti, L.G., 2012. The α1K276E startle disease mutation reveals multiple intermediate states in the gating of glycine receptors. J. Neurosci. 32, 1336–1352. https://doi.org/10.1523/jneurosci.4346-11.2012.

Marchetti, L., Porciani, D., Mitola, S., Giacomelli, C., 2022. Editorial: Molecular Insights into Ligand-Receptor Interactions on the Cell Surface, vol. 9, 921677. https://doi.org/10.3389/fmolb.2022.921677.

Mariqueo, T., Oliva, C., Barra, R., Castillo, K., Stehberg, J., 2023. ROLE OF GLYCINE RECEPTORS IN THE NEUROIMMUNE MODULATION OF THE CHRONIC PAIN, vol. 15, pp. S281–S282. https://doi.org/10.1016/j.ibneur.2023.08.494.

Maynard, S.A., Rostaing, P., Schaefer, N., Gemin, O., Candat, A., Dumoulin, A., et al., 2021. Identification of a Stereotypic Molecular Arrangement of Endogenous glycine Receptors at Spinal Cord Synapses, vol. 10. https://doi.org/10.7554/eLife.74441, 10.7554/eLife.74441.

McEwan, T., Robinson, P.C., 2021. A Systematic Review of the Infectious Complications of Colchicine and the Use of Colchicine to Treat Infections, vol. 51, pp. 101–112. https://doi.org/10.1016/j.semarthrit.2020.11.007.

Muñoz, B., Mariqueo, T., Murath, P., Peters, C., Yevenes, G.E., Moraga-Cid, G., et al., 2021. Modulatory Actions of the Glycine Receptor β Subunit on the Positive Allosteric Modulation of Ethanol in α2 Containing Receptors, vol. 14, 763868. https://doi.org/10.3389/fnmol.2021.763868.

Nimgampalle, M., Chakravarthy, H., Sharma, S., Shree, S., Bhat, A.R., Pradeepkiran, J.A., et al., 2023. Neurotransmitter Systems in the Etiology of Major Neurological Disorders: Emerging Insights and Therapeutic Implications, vol. 89, 101994. https://doi.org/10.1016/j.arr.2023.101994.

Oz, M., Yang, K.-H.S., Mahgoub, M.O., 2022. Effects of Cannabinoids on Ligand-Gated Ion Channels, vol. 13, 1041833. https://doi.org/10.3389/fphys.2022.1041833.

Perez-Leon, J.A., Espinal-Centeno, A., Mendoza-Gonzalez, Z., Camacho, A.C., Lopez, A. B., Perez, R.A., et al., 2022. Identification of Amacrine Neurons with a Glycinergic and GABAergic Phenotype in the Mouse Retina, vol. 10. https://doi.org/10.18103/mra.v10i1.2624.

Piro, I., Eckes, A.-L., Kasaragod, V.B., Sommer, C., Harvey, R.J., Schaefer, N., et al., 2021. Novel functional properties of missense mutations in the glycine receptor β subunit in startle disease. Front. Mol. Neurosci. 14. https://doi.org/10.3389/fnmol.2021.745275.

Rauschenberger, V., Piro, I., Kasaragod, V.B., Hörlin, V., Eckes, A.-L., Kluck, C.J., et al., 2023. Glycine receptor autoantibody binding to the extracellular domain is independent from receptor glycosylation. Front. Mol. Neurosci. 16. https://doi.org/10.3389/fnmol.2023.1089101.

Salceda, R., 2022. Glycine Neurotransmission: its Role in Development, vol. 16, 947563. https://doi.org/10.3389/fnins.2022.947563.

Sanli, E., Akbayir, E., Kuçukali, C.I., Baykan, B., Sirin, N.G., Bebek, N., et al., 2021. Adaptive Immunity Cells Are Differentially Distributed in the Peripheral Blood of glycine Receptor Antibody-Positive Patients with Focal Epilepsy of Unknown Cause, vol. 170, 106542. https://doi.org/10.1016/j.eplepsyres.2020.106542.

San Martin, V.P., Sazo, A., Utreras, E., Moraga-Cid, G., Yevenes, G.E., 2022. Glycine Receptor Subtypes and Their Roles in Nociception and Chronic Pain, vol. 15, 848642. https://doi.org/10.3389/fnmol.2022.848642.

Sawant, A., Ebbinghaus, B.N., Bleckert, A., Gamlin, C., Yu, W.-Q., Berson, D., et al., 2021. Organization and Emergence of a Mixed GABA-glycine Retinal Circuit that Provides Inhibition to Mouse ON-Sustained Alpha Retinal Ganglion Cells, vol. 34, 108858. https://doi.org/10.1016/j.celrep.2021.108858.

Schaefer, N., Harvey, R.J., Villmann, C., 2023. Startle Disease: New Molecular Insights into an Old Neurological Disorder, vol. 29, pp. 767–781. https://doi.org/10.1177/10738584221104724.

Schmiedhofer, P., Vogel, F.D., Koniuszewski, F., Ernst, M., 2022. Cys-loop Receptors on Cannabinoids: All High?, vol. 13, 1044575. https://doi.org/10.3389/fphys.2022.1044575.

Scott, S., Lynch, J.W., Keramidas, A., 2015. Correlating structural and energetic changes in glycine receptor activation. J. Biol. Chem. 290, 5621–5634. https://doi.org/10.1074/jbc.m114.616573.

Shahsavar, A., Stohler, P., Bourenkov, G., Zimmermann, I., Siegrist, M., Guba, W., et al., 2021. Structural Insights into the Inhibition of glycine Reuptake, vol. 591, pp. 677–681. https://doi.org/10.1038/s41586-021-03274-z.

Shi, S., Lefebvre, S.N., Peverini, L., Cerdan, A.H., Milan Rodriguez, P., Gielen, M., et al., 2023. Illumination of a Progressive Allosteric Mechanism Mediating the glycine Receptor Activation, vol. 14. https://doi.org/10.1038/s41467-023-36471-7, 795-023-36471–7.

Valdés-Jorquera, R., Oviedo-Castro, L., Oliva, C.A., Mariqueo, T.A., 2022. Role of Glycine and Glycine Receptors in Vascular Endothelium: A New Perspective for the Management of the Post-Ischemic Injury, vol. 20, pp. 221–229. https://doi.org/10.2174/1570161120666220720101352.

Wei, H., Chen, Z., Koivisto, A., Pertovaara, A., 2021. Spinal Mechanisms Contributing to the Development of Pain Hypersensitivity Induced by Sphingolipids in the Rat, vol. 73, pp. 672–679. https://doi.org/10.1007/s43440-020-00207-x.

Wiessler, A.-L., Talucci, I., Piro, I., Seefried, S., Hörlin, V., Baykan, B.B., et al., 2024. Glycine Receptor β-Targeting Autoantibodies Contribute to the Pathology of Autoimmune Diseases, vol. 11, e200187. https://doi.org/10.1212/NXI.0000000000200187.

Wildman, S.S., Dunn, K., Van Beusecum, J.P., Inscho, E.W., Kelley, S., Lilley, R.J., et al., 2023. A Novel Functional Role for the Classic CNS Neurotransmitters, GABA, glycine, and Glutamate, in the Kidney: Potent and Opposing Regulators of the Renal Vasculature, vol. 325, pp. F38–F49. https://doi.org/10.1152/ajprenal.00425.2021.

Wu, J., Zhao, M., Jin, Y., Li, M., Yu, K., Yu, H., 2023. Schisandrin B, a dual positive allosteric modulator of GABAA and glycine receptors, alleviates seizures in multiple mouse models. Acta Pharmacol. Sin. 45, 465–479. https://doi.org/10.1038/s41401-023-01195-3.

Yu, H., Bai, X.-C., Wang, W., 2021. Characterization of the Subunit Composition and Structure of Adult Human glycine Receptors, vol. 109, pp. 2707–2716.e6. https://doi.org/10.1016/j.neuron.2021.08.019.

Yu, J., Zhu, H., Lape, R., Greiner, T., Du, J., Lu, W., et al., 2021. Mechanism of Gating and Partial Agonist Action in the glycine Receptor, vol. 184, pp. 957–968.e21. https://doi.org/10.1016/j.cell.2021.01.026.

Zeilhofer, H.U., Werynska, K., Gingras, J., Yévenes, G.E., 2021. Glycine Receptors in Spinal Nociceptive Control—An Update, vol. 11, p. 846. https://doi.org/10.3390/biom11060846.

Zhan, F., Wang, S.-G., Cao, L., 2021. Advances in Hyperekplexia and Other Startle Syndromes, vol. 42, pp. 4095–4107. https://doi.org/10.1007/s10072-021-05493-8.

Zhang, Y., Keramidas, A., Lynch, J.W., 2016. The free zinc concentration in the synaptic cleft of artificial glycinergic synapses rises to at least 1 μm. Front. Mol. Neurosci. 9. https://doi.org/10.3389/fnmol.2016.00088.

Zhang, Y., Yu, D., Gong, X., Meng, C., Lv, J., Li, Q., 2024. Tropisetron Attenuates Neuroinflammation and Chronic Neuropathic Pain via α7nAChR Activation in the Spinal Cord in Rats, pp. 1–9. https://doi.org/10.1080/10790268.2022.2046923.

Zhu, H., 2022. Structure and Mechanism of Glycine Receptor Elucidated by Cryo-Electron Microscopy, vol. 13, 925116. https://doi.org/10.3389/fphar.2022.925116.

Zhu, H., Gouaux, E., 2021. Architecture and Assembly Mechanism of Native glycine Receptors, vol. 599, pp. 513–517. https://doi.org/10.1038/s41586-021-04022-z.