The inhibitory glycine receptor is a ligand-gated chloride channel of the cys-loop receptor family. As a chloride-selective channel, it mediates rapid synaptic inhibition in mammalian spinal cord, brainstem, higher brain centres and nonneuronal tissues. In recent years, our understanding of glycine receptors has steadily grown, adding considerable depth to our knowledge of receptor function, structure, cellular trafficking and tissue distribution. Furthermore, new roles for glyciner ic transmission in higher brain function have been uncovered. Glycine receptors should no longer be considered only as mediators of spinal reflexes, but were also found to play an important role in the modulation of higher brain function, including vision, hearing and pain signalling. The identification of novel agonists and modulators underlines the relevance of the inhibitory glycine receptor as a therapeutic target. This review extends a previous article of this series and highlights key developments in glycine receptor research over the past 2–3 years.

Introduction

The inhibitory glycine receptor (GlyR) is among the principal mediators of rapid synaptic inhibition in the mammalian spinal cord, brainstem and higher brain centres. It is a member of the cys-loop family of ligand-gated ion channel receptors, which includes nicotinic acetylcholine, GABA\textsubscript{A} and serotonin type 3 (5-HT\textsubscript{3}) receptors. Cys-loop receptor subunits are glycosylated integral membrane proteins with a molecular weight of 45–60 kD. Five identical or homologous subunits assemble into pentameric transmembrane complexes that surround a central ion pore which opens transiently upon binding of the activating ligand. In the case of the glycine receptor, five subunits (\(\alpha_1–\alpha_4, \beta\)) have been identified to date. Under physiological conditions, the glycine receptor channel is selective for anions, primarily chloride, leading to postsynaptic hyperpolarization. A depolarising action of glycine receptors was reported, depending on extra- and intracellular chloride concentration, that is, the direction of chloride flux. Loss-of-function mutations in glycine receptor genes underlie complex motor disorders, such as human hyperekplexia (STHE, startle disease, OMIM 149400), stiff man syndrome, bovine myoclonus and other neuromuscular diseases. In recent years, the traditional view of glycine receptors as inhibitory transmitters on the spinal cord level had to be extended, as GlyRs were found in higher brain centres including retina, cochlea or hippocampus. Furthermore, glyciner ic transmission has been demonstrated to be an integral part of pain signalling. Glycine receptors are being targeted by various neuromodulators, alcohols and anaesthetics, and remain an attractive target for drug discovery.

Glycine receptors form functional homomeric channels, which can readily be studied in recombinant systems, in vitro data from recombinant receptors usually correlate well with in vivo measurements and results obtained from acute or cultured neurons. The alkaloid strychnine is a highly selective and potent inhibitor and valuable affinity ligand for pharmacological studies as GlyRs are its exclusive target. This has made the glycine receptor a viable model for genetics and structure–function analysis of ligand-gated ion channels and their associated function in the nervous system.
Glycine Receptor Subunits, Topology and Function

Glycine receptors were among the first ion channel proteins to be isolated from mammalian nervous tissue. These preparations were possible due to the availability of the selective high-affinity ligand strychnine ($K_D$ in the nM range), which allowed affinity purification of the receptor protein. Studies from the Betz laboratory identified the pentameric assembly of subunits and confirmed the typical topology of the receptor. To date, four alpha subunits of approximately 48 kD have been identified, with GLRA4 being expressed in chick only, the corresponding gene GLRA4 is considered a pseudogene in mammals (Lynch, 2009). The beta subunit (58 kD) mediates cytoskeletal anchoring of the receptor complex, and was for some time considered to be only ‘structural’, not contributing to channel activity per se. This view had to be revised, as Glycine receptor subunit beta (GLRB) mutations were shown to have functional implications that were observed in both, recombinant systems and primary neurons, highlighting a significant contribution of the beta subunit to channel function. See also: Glycine Receptors

GlyR subunits share topology with other members of the cys-loop receptor family: about half the protein forms the N-terminal extracellular domain (ECD), followed by four helical transmembrane segments (TM), all some 20–23 residues long (Figure 1). The TM1–2 loop and TM2–3 loop are short, comprising approximately 8 and 15 residues.

![Figure 1](image_url)

**Figure 1** Schematic drawing of glycine receptor topology. (a) Side view of receptor complex. (b) Top view of receptor, pore-lining TM2 is shaded. (c) Topology of one receptor subunit. Secondary structures and mutations in the receptor protein are indicated after modelled structures (see Legendre et al., 2009; Yevenes and Zeilhofer, 2011). ⬤, ethanol-sensitive residues (A52, S267, A288-TM3, K385/K386); ■, Zn$^{2+}$-sensitive residues (D80, E192, E194); ▲, Tropine modulation (Q67, R119, S129); ○, Anaesthetic-sensitive residues (S267, A288-TM3); □, Ivermectin interaction (A288-TM3); ◇, THC modulation (S296-TM3).
respectively. Although short, they contain residues that are critical determinants of receptor channel function (Breitinger and Becker, 2002; Lynch, 2004; Bode and Lynch, 2014). TM2 forms the inner lining of the central ion pore (Figure 1). Numerous contributions of individual residues and segments of TM2 to channel function have been identified (Lynch, 2004). The large (80–100 residues) intracellular loop between TM3 and 4 contains functional sites for intracellular modulations such as ubiquitination, cytoskeletal attachment, phosphorylation and binding of intracellular ligands (Breitinger and Becker, 2002). This domain is the region of highest diversity between the closely related GlyR subunits. While ligand binding obviously takes place at the N-terminal domain, it has been shown that regions all over the receptor protein contribute to ion channel function, including some that are quite far from both, the ligand-binding site, and the ion pore. A region within the intracellular TM3–4 domain, which is alternatively spliced in z3L and z3K receptors was shown to be a determinant of ion channel gating. A basic motif (KKKKK), located near the TM3 end of the intracellular TM3–4 loop, was found to constitute an active nuclear import signal (Dutertre et al., 2012). A functional residue study showed that truncation of the glycine receptor before TM4 leads to inactive fragments, but co-expression of TM4 and the C-terminus restored functional channels (Dutertre et al., 2012). Interactions between TM4 and the other transmembrane segments are a relevant contribution to the stabilisation of receptor transmembrane topology. See also: Glycine Receptors; Ligand-Gated Ion Channels

Glycine receptors are transmembrane chloride channels. Traditionally, ligand-gated ion channel function is monitored by patch-clamp electrophysiology techniques. Except for cell-attached patch recordings these methods are invasive, that is, the cell interior is altered in the experiment. In recent years, chloride-sensitive fluorescent dyes have been developed, which allow the monitoring of intracellular chloride levels. Such optical probes of ion channel activity provide an additional, noninvasive analytical tool (Bregestovski et al., 2009). Glycine receptors themselves have even been used as measuring devices, when glycine receptor-carrying membranes were immobilised on sensor chips. Anion conductance through these immobilised channels is the primary signal and such biosensors could be used to monitor glycine concentrations (Sommerhage et al., 2010). See also: Patch-Clamp Technique

Tissue Distribution and Development of Glycinergic Transmission

Glycine receptors in the CNS

Glycine receptors were first identified in lower brain regions, especially spinal cord and brainstem. Over the years, GlyRs were found on transcript and protein levels in numerous regions of the central nervous system (CNS), including forebrain, hippocampus, hypothalamus and medial vestibular neurons, where GlyRs help to maintain overall synaptic excitability (Baer et al., 2009). Glycine receptors in the hippocampus are heavily regulated during development with respect to subunit composition and synaptic versus extrasynaptic localisation (Aroeira et al., 2010). The role of extrasynaptic glycine and gamma-aminobutyric acid (GABA) receptors, and the paracrine effects of glycine and GABA during development have been reviewed (Le-Corrone et al., 2011). In forebrain, z2 is not replaced by z1 during development but remains the dominant subunit, only the β subunit is upregulated (Jonsson et al., 2012).

GlyRs were detected in centres involved in brain reward and emotional processing, where glycine, taurine and ethanol (a GlyR modulator) affect dopaminergic transmission (Adermark et al., 2011). Splice variants of hippocampal z3 glycine receptors showed different association with glutamatergic terminals, and a key role for GlyR splicing was suggested for the pathology of temporal lobe epilepsy (Eichler et al., 2009).

Respiratory rhythm generation in the pre-Boetzinger complex involves glycine receptor-mediated inhibition; the complex network of respiration in medulla and pons involves several transmitter systems, and the participation of z3 glycine receptors as well as a crucial role of z3 phosphorylation through metabotropic serotonin 5-HT1A receptors has been demonstrated (Ren and Greer, 2008).

The distribution of GlyR β subunits in the brain was probed with a beta-specific monoclonal antibody. GLRB messenger ribonucleic acid (mRNA) transcripts were found in spinal cord, brainstem, midbrain, olfactory cortex, neocortex, cerebellum and hippocampus. In contrast, GlyR β protein immunoreactivity was only detected in spinal cord, brainstem, midbrain and olfactory cortex, suggesting an absence of efficient translation in the other regions (Weltzien et al., 2012).

Glycine receptors in the retina

Glycine receptors show a distinct pattern of distribution across retinal layers, indicating a significant contribution to vision, mainly through amacrine cells. A detailed description of glycine receptor subtypes, their distribution in the retina and their contribution to retinal transmission was delineated using a combination of subtype-specific antibodies and knockout animals lacking z1, z2, or z3 subunits (Wassle et al., 2009). The subclassification of amacrine cells, their synaptic connections to bipolar, ganglion and amacrine cells as well as the mechanisms of GABAergic and glycinergic transmission in the visual process were recently summarised (Zhang and McCall, 2012).

Glycine receptors in cochlea

Glycine receptors contribute to auditory processes in both cochlea and higher auditory centres (Wang et al., 2009).
This was confirmed when z1 glycine receptor subunits were identified in the cochlea (Buerbank et al., 2011).

**Extraneuronal glycine receptors**

Neuronal-type glycine receptors have been identified on human and porcine sperm, where they are suggested to be involved in the acrosome reaction (Kumar and Meizel, 2008). Macrophages such as Kupffer cells from the liver, peritoneal neutrophils, as well as splenic and alveolar macrophages have been shown to express functional GlyR channels (Froh et al., 2002). Recently, glycine receptors were identified on neonatal rat cardiomyocytes, where they interfere with lipopolysaccharides (LPS)-induced intracellular signalling (Wang et al., 2009), and in smooth airway muscle, where they control excitability and relaxation (Yim et al., 2011).

Glycine receptors have been found in various other nonneuronal tissues and cells, including immune cells, endothelial cells, renal cells, hepatocytes and macroglia where they mediate cytoprotective and anti-ischaemic effects. It was suggested, however, that these activities were not mediated by the glycine receptor-associated chloride channel, but due to a different, nonchannel mode of GlyR action (den Eynden et al., 2009).

**Non-roden animal models**

In addition to the murine model which has been an invaluable tool in the identification of glycine receptor function and distribution (Schaefer et al., 2013), the zebrafish (*Brachydanio rerio*) has been introduced for the study of *in vivo* glycine receptors and developmental changes in glycinerergic transmission (Ganser and Dallman, 2009). GlyR defect mutants and development in zebrafish have been reviewed, showing that indeed GlyR defects in zebrafish and mouse lead to comparable phenotypes (Ganser and Dallman, 2009).

**Glycine receptor trafficking and cytoskeletal anchoring**

During the initial studies on GlyR protein isolation, the anchoring protein gephyrin was discovered as a membrane-associated protein that co-precipitated with glycine receptors from spinal cord. Gephyrin was quickly established as cytoskeletal anchoring partner of glycine receptors and is nowadays seen as a major organiser of inhibitory glycinerergic and GABAergic synapses (Tretter et al., 2012). Landmark studies were the description of surface movement of glycine receptors in real time via light microscopy (Dumoulin et al., 2009). These studies established that synaptic glycine receptors are characterised by slow lateral diffusion, which prolongs their sojourn in the synaptic site. Extending these observations, a dynamic model of synapse formation that relies on membrane motility and dwell-time of receptor complexes in synaptic sites has been developed (Haselwandter et al., 2011). The intracellular movement of GlyR subunits and other synaptic proteins continues to be an exciting and – literally – fast-moving field.

In addition to gephyrin, integrins and Ca^{2+}/calmodulin-dependent protein kinase II were shown by a fluorescence microscopy assay to regulate lateral diffusion and synapse formation of glycine receptors (Charrier et al., 2006). The trafficking proteins Vps35 (vacuolar protein sorting 35) and Nbea (neurobeachin) were shown to bind to GlyR β subunits (Dutertre et al., 2012). New cellular interaction partners for all glycine receptor subunits and gephyrin are being discovered (Charrier et al., 2010; Herweg and Schwarz, 2012) that are likely to expand the arsenal of proteins assisting with GlyR anchoring and trafficking.

Protein phosphorylation is yet another cellular mechanism that regulates membrane diffusion and function of glycine receptors. Multiple effects of phosphorylation on ion channel receptor function have been reviewed recently (Talwar and Lynch, 2014).

**Glycine Receptors in Pain Signalling**

GlyR activity in the transmission of pain signals involves crosstalk between glycinerergic and prostaglandin pathways. Recent reviews give a detailed overview of the spinal network composed of inhibitory and excitatory neurons involved in nociception and the role of fast inhibitory transmission in pain signalling (Lynch and Callister, 2006; Yevenes and Zeilhofer, 2011; Dutertre et al., 2012; Zeilhofer et al., 2012).

**Structure–Function Relations of Glycine Receptors**

High-resolution structures for membrane proteins are difficult to obtain. This is due to general difficulties in isolation of these proteins in sufficient amounts and the exquisite purity that is required for crystallisation and X-ray diffraction, or NMR studies. A second problem is the abundance of physiologically relevant subunit combinations which are difficult to reproduce in overexpression systems and preclude homogenous preparation of one single protein species that is needed for structure determination. Even if homomeric receptors are used, ligand-gated ion channels adopt several distinct conformational states that are associated with their function, and may coexist at any given time. Structure determination, however, requires a homogenous preparation, ideally of only one conformer. Despite these intrinsic difficulties, impressive progress has been made in the field of structural analysis of membrane proteins, including ion channels. Structure determination of ligand-gated ion channels was pioneered by the electron microscopy imaging data of Nigel Unwin's group on muscle-type acetylcholine receptors that were isolated from the electric organ of the electric ray *Torpedo*.
californica and eel Electrophorus electricus (Unwin, 2013). It should be noted that these structures – being the only ones available at the time – were guiding the entire field of ion channel structure and topology analysis for years. Only recently, valid crystal structures have been achieved, starting with the acetylcholine binding protein (AChBP), which resembles the N-terminal ECD of the cys-loop receptor families, to the atomic resolution structures of bacterial and eukaryotic receptors that are available today (Corringer et al., 2010; Dutertre et al., 2012; Dacosta and Baenziger, 2013).

In addition to the AChBP, X-ray structures at atomic resolution of two bacterial proton-gated channels, GLIC (gloeobacter ligand-gated ion channel) and ELIC (Erwinia chrysanthemi ligand-gated ion channel), have provided new insight into cys-loop receptor structure, as their structure and mechanism of function are closely related to higher members of the cys-loop receptor family (Corringer et al., 2010). The relation of structural changes and channel activation of cys-loop receptors, as well as their application to the channel gating mechanism and allosteric regulation have been the subject of recent reviews (Corringer et al., 2010; Dacosta and Baenziger, 2013). Using the growing number of high-resolution structures, a high-throughput modelling approach was developed, where structures of all related cys-loop receptors are superimposed with the aim to identify common patterns and structures as well as functionally relevant regions and domains of the cys-loop receptor family (Mullins et al., 2010). See also: Ligand-Gated Ion Channels

In contrast to the difficulties obtaining structural information, access to the function of ion channels has been easier. Since the first electrophysiological studies in the 1950s, the function of ion channel receptors was studied by means of patch-clamp recording techniques. Thus, structure–function relationships have remained one of the key fields of research in the membrane receptor field. This led to the situation that a great deal about ion channel function and pharmacology, and about the effect of point mutations on channel function were known without knowledge of the corresponding protein structures. To date, biochemical analysis (i.e. mutagenesis) in combination with patch-clamp electrophysiology remains one of the core areas of ion channel research. From detailed single-channel analysis, a modified mechanism for channel gating has been proposed, where the glycine receptor channel binds the agonist, then first enters an activated state (Flip state), from which channel opening can occur. In the sequence Resting—Flipped—Open, agonist affinity would increase for a full agonist, whereas partial agonists would be less effective in promoting the channel from resting to flipped conformation (Sivilotti, 2010). Finally, RNA editing was shown to be a further physiological mechanism of GlyR regulation. Editing of brain z3 glycine receptor RNA transcripts generated a novel GlyR variant with an approximately 10-fold lower EC\textsubscript{50} than the wildtype (Legendre et al., 2009). See also: Ligand-Gated Ion Channels; Patch-Clamp Technique

Opening of the GlyR channel after binding of agonist requires a conformational change in the receptor protein. Over the years, numerous amino acid residues involved in this conformational change have been identified. Homology modelling based on available structures (of the AChBP or AChR ECDs) has guided these studies. Agonist binding on cys-loop receptors is taken to occur on the interface between two subunits, with protein loops from both subunits forming the agonist binding site (Lynch, 2004; Corringer et al., 2010; Dacosta and Baenziger, 2013). The combination of patch-clamp analysis and fluorometry of receptors with fluorescence-labelled domains revealed movements in some (not all) of the known loops of the GlyR ECD upon activation. The extent of these domain movements correlated with efficacy of the tested agonists (Dutertre et al., 2012). Different subunits of the pentameric complex of cys-loop receptors contribute differently (i.e. asymmetrically) to channel conductance, as shown by detailed single-channel analysis of concanameric glycine receptors of fixed stoichiometry (Moroni et al., 2011).

Many attempts have been made to dissect the complex conformational changes required for glycine receptor activation: ligand binding – channel-opening and gating – desensitization. These elementary processes can be separated kinetically, and recent advances in ion channel structure determination, combined with structure–function studies move towards a detailed molecular understanding of the workings of GlyR function. A complementary approach is the dissection of the relevant protein domains, which has been achieved for (1) the extracellular N-terminal domain, (2) the domain contacts that link ligand binding to gating and (3) the channel lining TM2.

1. When the ECD of the bacterial channel GLIC was fused to the transmembrane domain moiety of the z1 GlyR, the resulting chimera was activated by protons but had showed all properties (conductance, modulation by membrane-associated drugs) of the GlyR channel. Thus, agonist binding and channel gating could be structurally dissected (Duret et al., 2011).

2. Recently, a link between the processes of ligand binding and channel gating has been proposed from detailed mechanistic analysis of glycine receptor activation. An additional state, termed the flip state, is populated upon ligand binding, and channel opening/closing (i.e. gating) only occurs from this flipped state (Sivilotti, 2010). The sequence of receptor activation should thus read: ligand binding–flipping–gating–desensitization.

3. As channel gating must be mediated through the interface between ligand-binding ECD and the transmembrane channel pore, interactions between residues at the interface of ligand binding- and transmembrane domains were studied in recombinant glycine receptors. Ionic and hydrophobic interactions were identified to be critical for channel gating (Pless et al., 2011). Removing electrostatic interactions by mutagenesis resulted in a constitutively open channel (Todorovic et al., 2010).
4. The solution NMR structure of artificial TM2 peptides of the GlyR was determined; these peptides are even able to form functional transmembrane chloride channels on their own and can be seen as minimalist transmembrane ion channels. Further, such peptides may be therapeutically useful, as they could restore lost chloride conductance in hyperekplexia and similar diseases (Herrera et al., 2010).

5. The final step in the functional cycle of ligand-gated ion channel receptors is desensitization, the decay of channel-mediated currents in the continued presence of activating ligand. Desensitization is an intrinsic “off-switch” of channel signalling (Breitinger and Becker, 2002). The transition, however, is slow compared to the other elementary processes of channel activation, and its physiological role is still unclear. A recent study used voltage-clamp fluorometry to follow movements of fluorescent labels during receptor activation and desensitization, and identified specific conformational rearrangements in the extracellular N-terminal domain and TM1 that constitute desensitization (Wang and Lynch, 2011).

Allosteric Modulation of Glycine Receptors

Allosteric modulation of signalling proteins is a crucial regulatory mechanism, since most commercial drugs act at allosteric sites. Two principal cases have to be differentiated, where (1) glycine receptors are the primary target, that is, the drug has the highest affinity for the GlyR, (2) the affinity for glycine receptors is lower, and other proteins are the primary physiological target of the compound. Several well-known drugs and pharmaceuticals were indeed found to have inhibitory effects on native and recombinant glycine receptors, the serotonin uptake inhibitor fluoxetine, to have inhibitory effects on native and recombinant glycine receptors, the serotonin uptake inhibitor fluoxetine, that is the drug has the highest affinity for the GlyR, (2) the affinity for glycine receptors is lower, and other proteins are the primary physiological target of the compound. Several well-known drugs and pharmaceuticals were indeed found to have inhibitory effects on native and recombinant glycine receptors, the serotonin uptake inhibitor fluoxetine being one example (Ye et al., 2008). These findings may not always be physiologically relevant, yet such inhibitors can be important tools for the identification of modulatory sites. Thus, high-throughput methods for the identification of novel glycineergic ligands were developed (Gilbert et al., 2009). Modulation of glycine receptors by cannabinoids and fatty acids was recently reviewed (Zhang and Xiong, 2009; Yevenes and Zeilhofer, 2011), and potent agonists and antagonists continue to be of major clinical and pharmacological relevance. Several recent reviews cover this field (Zhang and Xiong, 2009; Yevenes and Zeilhofer, 2011; Dutertre et al., 2012), and some examples have been included in the Further reading section.

Glycine Receptor Modulation by Ethanol

Ethanol was initially considered to be a general modulator of CNS function, altering membrane properties, not acting on specific target proteins. This view had to be changed, as specific binding partners for ethanol were identified, including inhibitory glycine receptors, where, ethanol was found to enhance glycine-mediated currents. Mechanisms and structural basis of the action of ethanol on GlyRs have been a subject in many reviews (Zhang and Xiong, 2009; Yevenes and Zeilhofer, 2011). Notably, administration of the unconventional GlyR agonist ivermectin into the ventral tegmental area lead to reduced alcohol intake in rats (Yardley et al., 2012), further evidence of a direct, physiological action of ethanol on glycine receptors.

Unconventional Agonists of the Glycine Receptor

To date, three classical GlyR agonists are known in the literature, glycine, taurine and β-alanine. The latter two are considered partial agonists, that is, with a less efficacious channel-opening equilibrium. There is, thus, a considerable interest in selective glycine receptor agonists for research and therapeutic applications. Ivermectin is the only specific and efficacious agonist of the glycine receptor that is not a close structural relative to glycine and does not target the strychnine-sensitive glycine site on the receptor. Originally discovered and isolated from Japanese soil as an anthelminthic, ivermectin has found worldwide use in treatment of parasitic infections in humans and farm animals. Its action against nematodes and other parasites results from an overactivation of chloride channels. Since its discovery as glycine receptor agonist, its mechanism of function, and its binding to the GlyR have been intensely studied. Mutation studies identified critical residues for ivermectin binding, proposing its binding site to be located on the interface between TM1 and TM3. Activation and modulation of cys-loop receptors by ivermectin has recently been reviewed (Lynagh and Lynch, 2012).

Recent reviews cover allosteric modulation of glycine receptors, including the effects of ethanol, anesthetics, zinc, tropine, cannabinoids and of the alternative agonist ivermectin (Zhang and Xiong, 2009; Yevenes and Zeilhofer, 2011). As intuitively expected, ethanol and zinc mainly target extracellular and transmembrane domains, although an indirect, G-protein-coupled-receptor (GPCR) – Gβγ – mediated effect on residues in the cytosolic TM3–4 loop has been identified (Yevenes and Zeilhofer, 2011). Hydrophobic agents, such as ivermectin and anesthetics, preferably target sites in the transmembrane region (Zhang and Xiong, 2009; Yevenes and Zeilhofer, 2011; see also Figure 1).

Glycine Receptors in Disease of the Nervous System

Ion channels are one of the major signalling devices in human physiology. Dysfunction of this essential system...
will almost inevitably result in pathological changes and disease. Channelopathies, therefore, are a field of highest clinical and pharmacological relevance, and have been studied extensively on the level of genetics, as well as on the protein (i.e. ion channel) level. Historically, the inhibitory glycine receptor was discovered as a spinal signalling device whose damage underlies the motor disorder hyperekplexia and other hypertonic diseases. Extensive reviews covering hyperekplexia, and related diseases have been published (Dreissen and Tijssen, 2012; Espay and Chen, 2013), including the contribution of the glycine receptor (Bode and Lynch, 2014), other associated genes (Davies et al., 2010) and corresponding murine models (Schaefer et al., 2013). A recent review article summarises currently known hyperekplexia mutations of the glycine receptor α1 and β subunit genes, GLRA1 and GLRB, where most mutations are found (Bode and Lynch, 2014). Thirty five of 55 STHE mutations in GLRA1 and GLRB are in the transmembrane region, and dominant mutations in GLRA1 cluster around TM2 (Bode and Lynch, 2014). Glycine transporters were found to be associated with hyperekplexia-related disorders. A defect in the glycine transporter GlyT2 was associated with hyperekplexia symptoms in Irish wolfhounds and cattle (James et al., 2012), although GlyT2 is also associated with neuronal diseases other than hyperekplexia. Autoimmunity against glycine receptors underlies stiff man syndrome (Butler et al., 2000) as well as progressive encephalomyelitis with rigidity and myoclonus – PERM (Iizuka et al., 2012). A participation of glycine receptors in a mouse model of amyotrophic lateral sclerosis has recently been discovered (Chang and Martin, 2011). See also: Glycine Receptors; Ion Channels and Human Disorders; Ion Channels; The Genetics of Neuronal Channelopathies

Conclusion

The inhibitory glycine receptor has proven to be an excellent model for a monogenic channelopathy, offering an easy combination of in vitro and in vivo assays. Recent years have seen a dramatic development and new roles of glycine receptors in higher brain centres, complex neuronal processes and even non-neuronal tissues were uncovered. Obviously, glycine receptors will remain an attractive field of research in the future.

Outlook

In addition to numerous well-known glycnergic agents, several recent studies identified substances that were known for various physiological activities to be GlyR modulators. Caffeine was found to inhibit glycine receptors, albeit with moderate affinity (IC50 ~ 500 μM). Direct inhibition of GABA_A and glycine receptors by androsterone and progesterone, and gingkoldiles was reported. The insecticides lindane and fipronil, as well as tutin, a neurotoxin isolated from the South American shrub Coriaria ruscifolia were inhibitors of glycine receptors. A mechanistic study identified synergisms - mutual potentiation of effects - between receptor inhibition by strychnine and the flavonoids genistein and quercetin. Finally, glutamate itself was reported to act as allosteric potentiator of glycine receptor currents, a finding that complements the long-known fact that glycine is a co-agonist at ionotropic N-methyl-D-aspartate (NMDA) glutamate receptors. The search for novel, specific glycine receptor modulators enjoys considerable interest from industry and basic research. Using marine organisms as sources for new pharmaceuticals, novel glycine receptor modulators of the family of ircinalactams were isolated from Australian marine sponges. From a phage display search for new GlyR modulators, a dodecapaeptide, YESIRIGVAPSQ, was identified that enhanced GlyR responses when co-applied with glycine at submaximal (EC10) concentrations. The field of glycine receptor pharmacology, allosterism, and identification of novel receptor ligands is of continued relevance and fascination.

References


### Further Reading


