

## Glycine receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Joseph. W. Lynch<sup>1</sup>, Lucia G. Sivilotti<sup>2</sup> and Trevor G. Smart<sup>2</sup>

1. University of Queensland, Australia
2. University College London, UK

### Abstract

The inhibitory glycine receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Glycine Receptors**) is a member of the Cys-loop superfamily of transmitter-gated ion channels that includes the zinc activated channels, GABA<sub>A</sub>, nicotinic acetylcholine and 5-HT<sub>3</sub> receptors [63]. The receptor is expressed either as a homo-pentamer of  $\alpha$  subunits, or a complex now thought to harbour 2 $\alpha$  and 3 $\beta$  subunits [30, 7], that contain an intrinsic anion channel. Four differentially expressed isoforms of the  $\alpha$ -subunit ( $\alpha$ 1- $\alpha$ 4) and one variant of the  $\beta$ -subunit ( $\beta$ 1, [GLRB](#), [P48167](#)) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for  $\alpha$ 1 ( $\alpha$ 1<sup>INS</sup> and  $\alpha$ 1<sup>del</sup>),  $\alpha$ 2 ( $\alpha$ 2A and  $\alpha$ 2B),  $\alpha$ 3 ( $\alpha$ 3S and  $\alpha$ 3L) and  $\beta$  ( $\beta$ Δ7) subunits and by mRNA editing of the  $\alpha$ 2 and  $\alpha$ 3 subunit [80, 91, 18]. Both  $\alpha$ 2 splicing and  $\alpha$ 3 mRNA editing can produce subunits (*i.e.*,  $\alpha$ 2B and  $\alpha$ 3P185L) with enhanced agonist sensitivity. Predominantly, the mature form of the receptor contains  $\alpha$ 1 (or  $\alpha$ 3) and  $\beta$  subunits while the immature form is mostly composed of only  $\alpha$ 2 subunits. RNA transcripts encoding the  $\alpha$ 4-subunit have not been detected in adult humans. The N-terminal domain of the  $\alpha$ -subunit contains both the agonist and [strychnine](#) binding sites that consist of several discontinuous regions of amino acids. Inclusion of the  $\beta$ -subunit in the pentameric glycine receptor contributes to agonist binding, reduces single channel conductance and alters pharmacology. The  $\beta$ -subunit also anchors the receptor, via an amphipathic sequence within the large intracellular loop region, to gephyrin. The latter is a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse [86, 51, 53]. G-protein  $\beta\gamma$  subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop [122, 121]. Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors [94]. Intracellular Ca<sup>2+</sup> appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation [24].

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##### glycine receptor $\beta$ subunit

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## References

1. Ahrens J, Demir R, Leuwer M, de la Roche J, Krampfl K, Foadi N, Karst M and Haeseler G. (2009) The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. *Pharmacology* **83**: 217-22 [PMID:19204413]
2. Aprison MH and Werman R. (1965) The distribution of glycine in cat spinal cord and roots *Life Sci.* **4**: 2075-83 [PMID:5866625]
3. Araki T, Yamano M, Murakami T, Wanaka A, Betz H and Tohyama M. (1988) Localization of glycine receptors in the rat central nervous system: an immunocytochemical analysis using monoclonal antibody. *Neuroscience* **25**: 613-24 [PMID:2840602]
4. Bakker MJ, van Dijk JG, van den Maagdenberg AM and Tijssen MA. (2006) Startle syndromes. *Lancet Neurol* **5**: 513-24 [PMID:16713923]
5. Balse E, Tessier LH, Forster V, Roux MJ, Sahel JA and Picaud S. (2006) Glycine receptors in a population of adult mammalian cones. *J. Physiol. (Lond.)* **571**: 391-401 [PMID:16396929]
6. Beato M, Groot-Kormelink PJ, Colquhoun D and Sivilotti LG. (2002) Openings of the rat recombinant alpha 1 homomeric glycine receptor as a function of the number of agonist molecules bound. *J. Gen. Physiol.* **119**: 443-66 [PMID:11981023]
7. Betz H and Laube B. (2006) Glycine receptors: recent insights into their structural organization and functional diversity. *J. Neurochem.* **97**: 1600-10 [PMID:16805771]
8. Bloomenthal AB, Goldwater E, Pritchett DB and Harrison NL. (1994) Biphasic modulation of the

- strychnine-sensitive glycine receptor by Zn<sup>2+</sup>. *Mol. Pharmacol.* **46**: 1156-9 [PMID:7808436]
9. Bormann J, Rundström N, Betz H and Langosch D. (1993) Residues within transmembrane segment M2 determine chloride conductance of glycine receptor homo- and hetero-oligomers. *EMBO J.* **12**: 3729-37 [PMID:8404844]
  10. Brejc K, van Dijk WJ, Smit AB and Sixma TK. (2002) The 2.7 Å structure of AChBP, homologue of the ligand-binding domain of the nicotinic acetylcholine receptor. *Novartis Found. Symp.* **245**: 22-9; discussion 29-32, 165-8 [PMID:12027010]
  11. Buckwalter MS, Cook SA, Davisson MT, White WF and Camper SA. (1994) A frameshift mutation in the mouse alpha 1 glycine receptor gene (Gla1) results in progressive neurological symptoms and juvenile death. *Hum. Mol. Genet.* **3**: 2025-30 [PMID:7874121]
  12. Burzomato V, Beato M, Groot-Kormelink PJ, Colquhoun D and Sivilotti LG. (2004) Single-channel behavior of heteromeric alpha1beta glycine receptors: an attempt to detect a conformational change before the channel opens. *J. Neurosci.* **24**: 10924-40 [PMID:15574743]
  13. Curtis DR, Hösl L and Johnston GA. (1967) Inhibition of spinal neurons by glycine. *Nature* **215**: 1502-3 [PMID:4293850]
  14. Curtis DR and Malik R. (1985) Glycine antagonism by RU 5135. *Eur. J. Pharmacol.* **110**: 383-4 [PMID:4007055]
  15. De Saint Jan D, David-Watine B, Korn H and Bregestovski P. (2001) Activation of human alpha1 and alpha2 homomeric glycine receptors by taurine and GABA. *J. Physiol. (Lond.)* **535**: 741-55 [PMID:11559772]
  16. Demir R, Leuwer M, de la Roche J, Krampfl K, Foadi N, Karst M, Dengler R, Haeseler G and Ahrens J. (2009) Modulation of glycine receptor function by the synthetic cannabinoid HU210. *Pharmacology* **83**: 270-4 [PMID:19307742]
  17. Dlugaiczyk J, Singer W, Schick B, Iro H, Becker K, Becker CM, Zimmermann U, Rohbock K and Knipper M. (2008) Expression of glycine receptors and gephyrin in the rat cochlea. *Histochem. Cell Biol.* **129**: 513-23 [PMID:18231803]
  18. Eichler SA, Kirischuk S, Jüttner R, Schafermeier PK, Legendre P, Lehmann TN, Gloveli T, Grantyn R and Meier JC. (2008) Glycinergic tonic inhibition of hippocampal neurons with depolarizing GABAergic transmission elicits histopathological signs of temporal lobe epilepsy. *J. Cell. Mol. Med.* **12**: 2848-66 [PMID:19210758]
  19. Findlay GS, Harris RA and Blednov YA. (2005) Male transgenic glycine receptor alpha1 (S267Q) mutant mice display a hyperekplexia-like increase in acoustic startle responses. *Pharmacol. Biochem. Behav.* **82**: 215-22 [PMID:16168470]
  20. Findlay GS, Phelan R, Roberts MT, Homanics GE, Bergeson SE, Lopreato GF, Mihic SJ, Blednov YA and Harris RA. (2003) Glycine receptor knock-in mice and hyperekplexia-like phenotypes: comparisons with the null mutant. *J. Neurosci.* **23**: 8051-9 [PMID:12954867]
  21. Findlay GS, Wick MJ, Mascia MP, Wallace D, Miller GW, Harris RA and Blednov YA. (2002) Transgenic expression of a mutant glycine receptor decreases alcohol sensitivity of mice. *J. Pharmacol. Exp. Ther.* **300**: 526-34 [PMID:11805213]
  22. Fritschy JM, Harvey RJ and Schwarz G. (2008) Gephyrin: where do we stand, where do we go? *Trends Neurosci.* **31**: 257-64 [PMID:18403029]
  23. Froh M, Thurman RG and Wheeler MD. (2002) Molecular evidence for a glycine-gated chloride channel in macrophages and leukocytes. *Am. J. Physiol. Gastrointest. Liver Physiol.* **283**: G856-63 [PMID:12223345]
  24. Fucile S, De Saint Jan D, de Carvalho LP and Bregestovski P. (2000) Fast potentiation of glycine receptor channels of intracellular calcium in neurons and transfected cells. *Neuron* **28**: 571-83 [PMID:11144365]
  25. Ge LH, Lee SC, Liu J and Yang XL. (2007) Glycine receptors are functionally expressed on bullfrog retinal cone photoreceptors. *Neuroscience* **146**: 427-34 [PMID:17346892]
  26. Greferath U, Brandstätter JH, Wässle H, Kirsch J, Kuhse J and Grünert U. (1994) Differential expression of glycine receptor subunits in the retina of the rat: a study using immunohistochemistry and in situ hybridization. *Vis. Neurosci.* **11**: 721-9 [PMID:7918222]

27. Grenningloh G, Pribilla I, Prior P, Multhaup G, Beyreuther K, Taleb O and Betz H. (1990) Cloning and expression of the 58 kd beta subunit of the inhibitory glycine receptor. *Neuron* **4**: 963-70 [PMID:2163264]
28. Grenningloh G, Rienitz A, Schmitt B, Methfessel C, Zensen M, Beyreuther K, Gundelfinger ED and Betz H. (1987) The strychnine-binding subunit of the glycine receptor shows homology with nicotinic acetylcholine receptors. *Nature* **328**: 215-20 [PMID:3037383]
29. Grenningloh G, Schmieden V, Schofield PR, Seeburg PH, Siddique T, Mohandas TK, Becker CM and Betz H. (1990) Alpha subunit variants of the human glycine receptor: primary structures, functional expression and chromosomal localization of the corresponding genes. *EMBO J.* **9**: 771-6 [PMID:2155780]
30. Grudzinska J, Schemm R, Haeger S, Nicke A, Schmalzing G, Betz H and Laube B. (2005) The beta subunit determines the ligand binding properties of synaptic glycine receptors. *Neuron* **45**: 727-39 [PMID:15748848]
31. Grünert U and Ghosh KK. (1999) Midget and parasol ganglion cells of the primate retina express the alpha1 subunit of the glycine receptor. *Vis. Neurosci.* **16**: 957-66 [PMID:10580731]
32. Grünert U and Wässle H. (1993) Immunocytochemical localization of glycine receptors in the mammalian retina. *J. Comp. Neurol.* **335**: 523-37 [PMID:8227534]
33. Han Y, Li P and Slaughter MM. (2004) Selective antagonism of rat inhibitory glycine receptor subunits. *J. Physiol. (Lond.)* **554**: 649-58 [PMID:14645455]
34. Handford CA, Lynch JW, Baker E, Webb GC, Ford JH, Sutherland GR and Schofield PR. (1996) The human glycine receptor beta subunit: primary structure, functional characterisation and chromosomal localisation of the human and murine genes. *Brain Res. Mol. Brain Res.* **35**: 211-9 [PMID:8717357]
35. Hartenstein B, Schenkel J, Kuhse J, Besenbeck B, Kling C, Becker CM, Betz H and Weiher H. (1996) Low level expression of glycine receptor beta subunit transgene is sufficient for phenotype correction in spastic mice. *EMBO J.* **15**: 1275-82 [PMID:8635460]
36. Harvey RJ, Depner UB, Wässle H, Ahmadi S, Heindl C, Reinold H, Smart TG, Harvey K, Schütz B and Abo-Salem OM *et al.*. (2004) GlyR alpha3: an essential target for spinal PGE2-mediated inflammatory pain sensitization. *Science* **304**: 884-7 [PMID:15131310]
37. Harvey RJ, Schmieden V, Von Holst A, Laube B, Rohrer H and Betz H. (2000) Glycine receptors containing the alpha4 subunit in the embryonic sympathetic nervous system, spinal cord and male genital ridge. *Eur. J. Neurosci.* **12**: 994-1001 [PMID:10762330]
38. Haverkamp S, Müller U, Zeilhofer HU, Harvey RJ and Wässle H. (2004) Diversity of glycine receptors in the mouse retina: localization of the alpha2 subunit. *J. Comp. Neurol.* **477**: 399-411 [PMID:15329889]
39. Hawthorne R, Cromer BA, Ng HL, Parker MW and Lynch JW. (2006) Molecular determinants of ginkgolide binding in the glycine receptor pore. *J. Neurochem.* **98**: 395-407 [PMID:16805834]
40. Heads JA, Hawthorne RL, Lynagh T and Lynch JW. (2008) Structure-activity analysis of ginkgolide binding in the glycine receptor pore. *J. Neurochem.* **105**: 1418-27 [PMID:18221374]
41. Heinze L, Harvey RJ, Haverkamp S and Wässle H. (2007) Diversity of glycine receptors in the mouse retina: localization of the alpha4 subunit. *J. Comp. Neurol.* **500**: 693-707 [PMID:17154252]
42. Hejazi N, Zhou C, Oz M, Sun H, Ye JH and Zhang L. (2006) Delta9-tetrahydrocannabinol and endogenous cannabinoid anandamide directly potentiate the function of glycine receptors. *Mol. Pharmacol.* **69**: 991-7 [PMID:16332990]
43. Hibbs RE and Gouaux E. (2011) Principles of activation and permeation in an anion-selective Cys-loop receptor. *Nature* **474**: 54-60 [PMID:21572436]
44. Hilf RJ and Dutzler R. (2008) X-ray structure of a prokaryotic pentameric ligand-gated ion channel. *Nature* **452**: 375-9 [PMID:18322461]
45. Hirzel K, Müller U, Latal AT, Hülsmann S, Grudzinska J, Seeliger MW, Betz H and Laube B. (2006) Hyperekplexia phenotype of glycine receptor alpha1 subunit mutant mice identifies Zn(2+) as an essential endogenous modulator of glycinergic neurotransmission. *Neuron* **52**: 679-90 [PMID:17114051]
46. Holland KD, Fleming MT, Cheek S, Moran JL, Beier DR and Meisler MH. (2006) De novo exon duplication in a new allele of mouse Glra1 (spasmodic). *Genetics* **174**: 2245-7 [PMID:17028313]
47. Howard RJ, Murail S, Ondricek KE, Corringer PJ, Lindahl E, Trudell JR and Harris RA. (2011) Structural

- basis for alcohol modulation of a pentameric ligand-gated ion channel. *Proc. Natl. Acad. Sci. U.S.A.* **108**: 12149-54 [PMID:21730162]
48. Jensen AA and Kristiansen U. (2004) Functional characterisation of the human alpha1 glycine receptor in a fluorescence-based membrane potential assay. *Biochem. Pharmacol.* **67**: 1789-99 [PMID:15081878]
  49. Kingsmore SF, Giros B, Suh D, Bieniarz M, Caron MG and Seldin MF. (1994) Glycine receptor beta-subunit gene mutation in spastic mouse associated with LINE-1 element insertion. *Nat. Genet.* **7**: 136-41 [PMID:7920630]
  50. Kingsmore SF, Suh D and Seldin MF. (1994) Genetic mapping of the glycine receptor alpha 3 subunit on mouse chromosome 8. *Mamm. Genome* **5**: 831-2 [PMID:7894176]
  51. Kirsch J. (2006) Glycinergic transmission. *Cell Tissue Res.* **326**: 535-40 [PMID:16807723]
  52. Kling C, Koch M, Saul B and Becker CM. (1997) The frameshift mutation oscillator (Glr1(sp-d-ot)) produces a complete loss of glycine receptor alpha1-polypeptide in mouse central nervous system. *Neuroscience* **78**: 411-7 [PMID:9145798]
  53. Kneussel M and Loebrich S. (2007) Trafficking and synaptic anchoring of ionotropic inhibitory neurotransmitter receptors. *Biol. Cell* **99**: 297-309 [PMID:17504238]
  54. Kondratskaya EL, Betz H, Krishtal OA and Laube B. (2005) The beta subunit increases the ginkgolide B sensitivity of inhibitory glycine receptors. *Neuropharmacology* **49**: 945-51 [PMID:16125206]
  55. Kruger W, Gilbert D, Hawthorne R, Hryciw DH, Frings S, Poronnik P and Lynch JW. (2005) A yellow fluorescent protein-based assay for high-throughput screening of glycine and GABAA receptor chloride channels. *Neurosci. Lett.* **380**: 340-5 [PMID:15862914]
  56. Kuhse J, Kuryatov A, Maulet Y, Malosio ML, Schmieden V and Betz H. (1991) Alternative splicing generates two isoforms of the alpha 2 subunit of the inhibitory glycine receptor. *FEBS Lett.* **283**: 73-7 [PMID:1645300]
  57. Kuhse J, Schmieden V and Betz H. (1990) Identification and functional expression of a novel ligand binding subunit of the inhibitory glycine receptor. *J. Biol. Chem.* **265**: 22317-20 [PMID:2176214]
  58. Kumar DV, Nighorn A and St John PA. (2002) Role of Nova-1 in regulating alpha2N, a novel glycine receptor splice variant, in developing spinal cord neurons. *J. Neurobiol.* **52**: 156-65 [PMID:12124753]
  59. Laube B, Kuhse J, Rundström N, Kirsch J, Schmieden V and Betz H. (1995) Modulation by zinc ions of native rat and recombinant human inhibitory glycine receptors. *J. Physiol. (Lond.)* **483 ( Pt 3)**: 613-9 [PMID:7776247]
  60. Laube B, Langosch D, Betz H and Schmieden V. (1995) Hyperekplexia mutations of the glycine receptor unmask the inhibitory subsite for beta-amino-acids. *Neuroreport* **6**: 897-900 [PMID:7542038]
  61. Laube B, Maksay G, Schemm R and Betz H. (2002) Modulation of glycine receptor function: a novel approach for therapeutic intervention at inhibitory synapses? *Trends Pharmacol. Sci.* **23**: 519-27 [PMID:12413807]
  62. Lozovaya N, Yatsenko N, Beketov A, Tsintsadze T and Burnashev N. (2005) Glycine receptors in CNS neurons as a target for nonretrograde action of cannabinoids. *J. Neurosci.* **25**: 7499-506 [PMID:16107637]
  63. Lynch JW. (2009) Native glycine receptor subtypes and their physiological roles. *Neuropharmacology* **56**: 303-9 [PMID:18721822]
  64. Lynch JW. (2004) Molecular structure and function of the glycine receptor chloride channel. *Physiol. Rev.* **84**: 1051-95 [PMID:15383648]
  65. Lynch JW and Chen X. (2008) Subunit-specific potentiation of recombinant glycine receptors by NV-31, a bilobalide-derived compound. *Neurosci. Lett.* **435**: 147-51 [PMID:18329806]
  66. Lynch JW, Jacques P, Pierce KD and Schofield PR. (1998) Zinc potentiation of the glycine receptor chloride channel is mediated by allosteric pathways. *J. Neurochem.* **71**: 2159-68 [PMID:9798943]
  67. Lynch JW, Rajendra S, Barry PH and Schofield PR. (1995) Mutations affecting the glycine receptor agonist transduction mechanism convert the competitive antagonist, picrotoxin, into an allosteric potentiator. *J. Biol. Chem.* **270**: 13799-806 [PMID:7775436]
  68. Lynch JW, Rajendra S, Pierce KD, Handford CA, Barry PH and Schofield PR. (1997) Identification of intracellular and extracellular domains mediating signal transduction in the inhibitory glycine receptor

- chloride channel. *EMBO J.* **16**: 110-20 [PMID:9009272]
69. Machu TK. (1998) Colchicine competitively antagonizes glycine receptors expressed in *Xenopus* oocytes. *Neuropharmacology* **37**: 391-6 [PMID:9681937]
70. Machu TK, Mihic SJ and Dildy-Mayfield JE. (1998) Selective actions of a detergent on ligand-gated ion channels expressed in *Xenopus* oocytes. *J. Pharmacol. Exp. Ther.* **284**: 32-6 [PMID:9435157]
71. Maksay G, Laube B and Betz H. (2001) Subunit-specific modulation of glycine receptors by neurosteroids. *Neuropharmacology* **41**: 369-76 [PMID:11522328]
72. Maksay G, Laube B and Betz H. (1999) Selective blocking effects of tropisetron and atropine on recombinant glycine receptors. *J. Neurochem.* **73**: 802-6 [PMID:10428078]
73. Maksay G, Laube B, Schemm R, Grudzinska J, Drwal M and Betz H. (2009) Different binding modes of tropeines mediating inhibition and potentiation of alpha1 glycine receptors. *J. Neurochem.* **109**: 1725-32 [PMID:19383091]
74. Malosio ML, Grenningloh G, Kuhse J, Schmieden V, Schmitt B, Prior P and Betz H. (1991) Alternative splicing generates two variants of the alpha 1 subunit of the inhibitory glycine receptor. *J. Biol. Chem.* **266**: 2048-53 [PMID:1703526]
75. Malosio ML, Marquèze-Pouey B, Kuhse J and Betz H. (1991) Widespread expression of glycine receptor subunit mRNAs in the adult and developing rat brain. *EMBO J.* **10**: 2401-9 [PMID:1651228]
76. Mangin JM, Nguyen L, Gougnard C, Hans G, Rogister B, Belachew S, Moonen G, Legendre P and Rigo JM. (2005) Developmental regulation of beta-carboline-induced inhibition of glycine-evoked responses depends on glycine receptor beta subunit expression. *Mol. Pharmacol.* **67**: 1783-96 [PMID:15722459]
77. Mascia MP, Mihic SJ, Valenzuela CF, Schofield PR and Harris RA. (1996) A single amino acid determines differences in ethanol actions on strychnine-sensitive glycine receptors. *Mol. Pharmacol.* **50**: 402-6 [PMID:8700149]
78. Mascia MP, Trudell JR and Harris RA. (2000) Specific binding sites for alcohols and anesthetics on ligand-gated ion channels. *Proc. Natl. Acad. Sci. U.S.A.* **97**: 9305-10 [PMID:10908659]
79. Matzenbach B, Maulet Y, Sefton L, Courtier B, Avner P, Guénet JL and Betz H. (1994) Structural analysis of mouse glycine receptor alpha subunit genes. Identification and chromosomal localization of a novel variant. *J. Biol. Chem.* **269**: 2607-12 [PMID:7507926]
80. Meier JC, Henneberger C, Melnick I, Racca C, Harvey RJ, Heinemann U, Schmieden V and Grantyn R. (2005) RNA editing produces glycine receptor alpha3(P185L), resulting in high agonist potency. *Nat. Neurosci.* **8**: 736-44 [PMID:15895087]
81. Melendrez CS and Meizel S. (1996) Immunochemical identification of the glycine receptor/Cl-channel in porcine sperm. *Biochem. Biophys. Res. Commun.* **223**: 675-8 [PMID:8687455]
82. Miller PS, Beato M, Harvey RJ and Smart TG. (2005) Molecular determinants of glycine receptor alphabeta subunit sensitivities to Zn<sup>2+</sup>-mediated inhibition. *J. Physiol. (Lond.)* **566**: 657-70 [PMID:15905212]
83. Miller PS, Da Silva HM and Smart TG. (2005) Molecular basis for zinc potentiation at strychnine-sensitive glycine receptors. *J. Biol. Chem.* **280**: 37877-84 [PMID:16144831]
84. Miller PS, Harvey RJ and Smart TG. (2004) Differential agonist sensitivity of glycine receptor alpha2 subunit splice variants. *Br. J. Pharmacol.* **143**: 19-26 [PMID:15302677]
85. Miyazawa A, Fujiyoshi Y and Unwin N. (2003) Structure and gating mechanism of the acetylcholine receptor pore. *Nature* **423**: 949-55 [PMID:12827192]
86. Moss SJ and Smart TG. (2001) Constructing inhibitory synapses. *Nat. Rev. Neurosci.* **2**: 240-50 [PMID:11283747]
87. Mülhardt C, Fischer M, Gass P, Simon-Chazottes D, Guénet JL, Kuhse J, Betz H and Becker CM. (1994) The spastic mouse: aberrant splicing of glycine receptor beta subunit mRNA caused by intronic insertion of L1 element. *Neuron* **13**: 1003-15 [PMID:7946325]
88. Nguyen L, Malgrange B, Belachew S, Rogister B, Rocher V, Moonen G and Rigo JM. (2002) Functional glycine receptors are expressed by postnatal nestin-positive neural stem/progenitor cells. *Eur. J. Neurosci.* **15**: 1299-305 [PMID:11994124]

89. Nikolic Z, Laube B, Weber RG, Lichter P, Kioschis P, Poustka A, Mülhardt C and Becker CM. (1998) The human glycine receptor subunit alpha3. Gria3 gene structure, chromosomal localization, and functional characterization of alternative transcripts. *J. Biol. Chem.* **273**: 19708-14 [PMID:9677400]
90. Nury H, Van Renterghem C, Weng Y, Tran A, Baaden M, Dufresne V, Changeux JP, Sonner JM, Delarue M and Corringer PJ. (2011) X-ray structures of general anaesthetics bound to a pentameric ligand-gated ion channel. *Nature* **469**: 428-31 [PMID:21248852]
91. Oertel J, Villmann C, Kettenmann H, Kirchhoff F and Becker CM. (2007) A novel glycine receptor beta subunit splice variant predicts an unorthodox transmembrane topology. Assembly into heteromeric receptor complexes. *J. Biol. Chem.* **282**: 2798-807 [PMID:17145751]
92. Pfeiffer F, Graham D and Betz H. (1982) Purification by affinity chromatography of the glycine receptor of rat spinal cord. *J. Biol. Chem.* **257**: 9389-93 [PMID:6286620]
93. Pinto LH, Grünert U, Studholme K, Yazulla S, Kirsch J and Becker CM. (1994) Glycine receptors in the retinas of normal and spastic mutant mice. *Invest. Ophthalmol. Vis. Sci.* **35**: 3633-9 [PMID:8088953]
94. Pitt SJ, Sivilotti LG and Beato M. (2008) High intracellular chloride slows the decay of glycinergic currents. *J. Neurosci.* **28**: 11454-67 [PMID:18987182]
95. Pribilla I, Takagi T, Langosch D, Bormann J and Betz H. (1992) The atypical M2 segment of the beta subunit confers picrotoxinin resistance to inhibitory glycine receptor channels. *EMBO J.* **11**: 4305-11 [PMID:1385113]
96. Probst A, Cortés R and Palacios JM. (1986) The distribution of glycine receptors in the human brain. A light microscopic autoradiographic study using [3H]strychnine. *Neuroscience* **17**: 11-35 [PMID:3008022]
97. Rajendra S, Lynch JW, Pierce KD, French CR, Barry PH and Schofield PR. (1995) Mutation of an arginine residue in the human glycine receptor transforms beta-alanine and taurine from agonists into competitive antagonists. *Neuron* **14**: 169-75 [PMID:7826634]
98. Rees MI, Lewis TM, Kwok JB, Mortier GR, Govaert P, Snell RG, Schofield PR and Owen MJ. (2002) Hyperekplexia associated with compound heterozygote mutations in the beta-subunit of the human inhibitory glycine receptor (GLRB). *Hum. Mol. Genet.* **11**: 853-60 [PMID:11929858]
99. Rundström N, Schmieden V, Betz H, Bormann J and Langosch D. (1994) Cyanotriphenylborate: subtype-specific blocker of glycine receptor chloride channels. *Proc. Natl. Acad. Sci. U.S.A.* **91**: 8950-4 [PMID:8090751]
100. Ryan SG, Buckwalter MS, Lynch JW, Handford CA, Segura L, Shiang R, Wasmuth JJ, Camper SA, Schofield P and O'Connell P. (1994) A missense mutation in the gene encoding the alpha 1 subunit of the inhibitory glycine receptor in the spasmodic mouse. *Nat. Genet.* **7**: 131-5 [PMID:7920629]
101. Sassoè-Pognetto M, Wässle H and Grünert U. (1994) Glycinergic synapses in the rod pathway of the rat retina: cone bipolar cells express the alpha 1 subunit of the glycine receptor. *J. Neurosci.* **14**: 5131-46 [PMID:8046473]
102. Sato K, Zhang JH, Saika T, Sato M, Tada K and Tohyama M. (1991) Localization of glycine receptor alpha 1 subunit mRNA-containing neurons in the rat brain: an analysis using in situ hybridization histochemistry. *Neuroscience* **43**: 381-95 [PMID:1656320]
103. Sato Y, Son JH and Meizel S. (2000) The mouse sperm glycine receptor/chloride channel: cellular localization and involvement in the acrosome reaction initiated by glycine. *J. Androl.* **21**: 99-106 [PMID:10670525]
104. Saul B, Schmieden V, Kling C, Mülhardt C, Gass P, Kuhse J and Becker CM. (1994) Point mutation of glycine receptor alpha 1 subunit in the spasmodic mouse affects agonist responses. *FEBS Lett.* **350**: 71-6 [PMID:8062927]
105. Schmieden V, Kuhse J and Betz H. (1993) Mutation of glycine receptor subunit creates beta-alanine receptor responsive to GABA. *Science* **262**: 256-8 [PMID:8211147]
106. Shan Q, Haddrill JL and Lynch JW. (2001) Ivermectin, an unconventional agonist of the glycine receptor chloride channel. *J. Biol. Chem.* **276**: 12556-64 [PMID:11278873]
107. Simmonds MA and Turner JP. (1985) Antagonism of inhibitory amino acids by the steroid derivative RU5135. *Br. J. Pharmacol.* **84**: 631-5 [PMID:3986429]

108. Sontheimer H, Becker CM, Pritchett DB, Schofield PR, Grenningloh G, Kettenmann H, Betz H and Seeburg PH. (1989) Functional chloride channels by mammalian cell expression of rat glycine receptor subunit. *Neuron* **2**: 1491-7 [PMID:2483325]
109. Steinbach JH, Bracamontes J, Yu L, Zhang P and Covey DF. (2000) Subunit-specific action of an anticonvulsant thiobutyrolactone on recombinant glycine receptors involves a residue in the M2 membrane-spanning region. *Mol. Pharmacol.* **58**: 11-7 [PMID:10860922]
110. Supplisson S and Chesnoy-Marchais D. (2000) Glycine receptor beta subunits play a critical role in potentiation of glycine responses by ICS-205,930. *Mol. Pharmacol.* **58**: 763-70 [PMID:10999946]
111. Takahashi T, Momiyama A, Hirai K, Hishinuma F and Akagi H. (1992) Functional correlation of fetal and adult forms of glycine receptors with developmental changes in inhibitory synaptic receptor channels. *Neuron* **9**: 1155-61 [PMID:1281418]
112. van den Pol AN and Gorcs T. (1988) Glycine and glycine receptor immunoreactivity in brain and spinal cord. *J. Neurosci.* **8**: 472-92 [PMID:2892900]
113. Vandenberg RJ, Handford CA and Schofield PR. (1992) Distinct agonist- and antagonist-binding sites on the glycine receptor. *Neuron* **9**: 491-6 [PMID:1326295]
114. Webb TI and Lynch JW. (2007) Molecular pharmacology of the glycine receptor chloride channel. *Curr. Pharm. Des.* **13**: 2350-67 [PMID:17692006]
115. Werman R, Davidoff RA and Aprison MH. (1967) Inhibition of motoneurons by iontophoresis of glycine. *Nature* **214**: 681-3 [PMID:4292803]
116. Xiong W, Cheng K, Cui T, Godlewski G, Rice KC, Xu Y and Zhang L. (2011) Cannabinoid potentiation of glycine receptors contributes to cannabis-induced analgesia. *Nat. Chem. Biol.* **7**: 296-303 [PMID:21460829]
117. Yang Z, Aubrey KR, Alroy I, Harvey RJ, Vandenberg RJ and Lynch JW. (2008) Subunit-specific modulation of glycine receptors by cannabinoids and N-arachidonyl-glycine. *Biochem. Pharmacol.* **76**: 1014-23 [PMID:18755158]
118. Yang Z, Cromer BA, Harvey RJ, Parker MW and Lynch JW. (2007) A proposed structural basis for picrotoxinin and picrotin binding in the glycine receptor pore. *J. Neurochem.* **103**: 580-9 [PMID:17714449]
119. Yang Z, Ney A, Cromer BA, Ng HL, Parker MW and Lynch JW. (2007) Tropicisetron modulation of the glycine receptor: femtomolar potentiation and a molecular determinant of inhibition. *J. Neurochem.* **100**: 758-69 [PMID:17181559]
120. Yevenes GE, Moraga-Cid G, Avila A, Guzmán L, Figueroa M, Peoples RW and Aguayo LG. (2010) Molecular requirements for ethanol differential allosteric modulation of glycine receptors based on selective Gbetagamma modulation. *J. Biol. Chem.* **285**: 30203-13 [PMID:20647311]
121. Yevenes GE, Moraga-Cid G, Guzmán L, Haeger S, Oliveira L, Olate J, Schmalzing G and Aguayo LG. (2006) Molecular determinants for G protein betagamma modulation of ionotropic glycine receptors. *J. Biol. Chem.* **281**: 39300-7 [PMID:17040914]
122. Yevenes GE, Peoples RW, Tapia JC, Parodi J, Soto X, Olate J and Aguayo LG. (2003) Modulation of glycine-activated ion channel function by G-protein betagamma subunits. *Nat. Neurosci.* **6**: 819-24 [PMID:12858180]
123. Yevenes GE and Zeilhofer HU. (2011) Allosteric modulation of glycine receptors. *Br. J. Pharmacol.* **164**: 224-36 [PMID:21557733]
124. Young TL and Cepko CL. (2004) A role for ligand-gated ion channels in rod photoreceptor development. *Neuron* **41**: 867-79 [PMID:15046720]
125. Young-Pearse TL, Ivic L, Kriegstein AR and Cepko CL. (2006) Characterization of mice with targeted deletion of glycine receptor alpha 2. *Mol. Cell. Biol.* **26**: 5728-34 [PMID:16847326]
126. Zarkin MA, Wamsley JK and Kuhar MJ. (1981) Glycine receptor: light microscopic autoradiographic localization with [<sup>3</sup>H]strychnine. *J. Neurosci.* **1**: 532-47 [PMID:6286895]