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NLM Citation: Haverkamp S. Glycine Receptor Diversity in the Mammalian Retina. 2012 Mar 27. In: Kolb H, Fernandez E, Jones B, et al., editors. Webvision: The Organization of the Retina and Visual System [Internet]. Salt Lake City (UT): University of Utah Health Sciences Center; 1995-.
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Glycine Receptor Diversity in the Mammalian Retina

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Created: March 27, 2012.

1 Introduction

Glycine is a major inhibitory neurotransmitter in the mammalian central nervous system (CNS). Its receptors, the inhibitory glycine receptors (GlyRs), are ligand-gated chloride channels composed of ligand-binding α and β subunits (1, 2). In mature neurons, the activation of GlyRs allows for an influx of chloride ions into the cytoplasm, which hyperpolarizes the postsynaptic membrane and, thereby, reduces neuronal firing. Inversely, the blockade of GlyRs by the competitive antagonist strychnine causes overexcitation resulting in pain, muscle cramps and exaggerated startle responses (3). Apart from its major transmitter function in spinal cord and brainstem, glycine also mediates substantial inhibitory neurotransmission via glycinergic amacrine cells in the mammalian retina. Thus, the abundant and highly complex expression patterns of different GlyR subtypes in the inner plexiform layer create an appealing field of retinal research.

2 Structure of glycine receptors

The GlyR was the first neurotransmitter receptor protein to be isolated from the mammalian CNS. Purification of the GlyR from rat spinal cord by strychnine affinity chromatography revealed three distinct polypeptides of molecular mass 48, 58 and 98 kDa (4). The 48 and 58 kDa peptides were shown to correspond to the α1 and β subunits, respectively. The 98 kDa peptide was later identified as the cytoplasmic protein, gephyrin, which is essential for clustering GlyRs at postsynaptic densities via direct interactions between the GlyR β subunit and intracellular microtubules (5).

GlyRs are pentameric ligand-gated ion channel receptors of the Cys-loop family, which also include $GABA_{A/C}$ receptors, muscle and neuronal nicotinic acetylcholine receptors, and serotonin type 3 receptors. Members of this superfamily share a common proposed structure (Fig. 1). Each subunit consists of a large N-terminal extracellular domain, four transmembrane segments (TM1–TM4), a long intracellular loop connecting TM3 and TM4, and a short extracellular C-terminus. The second transmembrane segment, TM2, lines the inner ion pore which, in GlyRs and $GABA_{A/C}$ receptors, displays strict anion selectivity.

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Molecular cloning has revealed four genes encoding the α subunits (α1, α2, α3, α4) and only one gene encoding the β subunit (6, 7). In the adult organism, two copies of the α subunit and three copies of the β subunit form the pentameric receptor protein (8).

3. Developmental expression

Glycine is excitatory during embryonic development and around birth. The neonatal form of the GlyR is thought to be a homopentamer of α2 subunits that are mainly found extrasynaptically in vivo, whereas adult synaptic GlyRs are heteromeric αβ receptors. It seems that homomeric α2 GlyRs mediate a depolarizing glycine-gated chloride flux that in turn stimulates the calcium influx necessary for the development of numerous neuronal specializations, including glycinergic synapses (2, 9). Surprisingly, however, knockout of the α2 subunit has no obvious effect on neuronal development (10), whereas an α1 knockout (*Glra1*$^{spd\text{-}ot}$*"oscillator")* has severe consequences: mice appear normal until the 2nd postnatal week whereupon they show prolonged periods of rapid tremor, producing extreme rigor and stiffness, and die within 10 days (11, 12).

4. Glycinergic amacrine cells

In the retina, approximately half of the amacrine cells release glycine at their synapses with bipolar, other amacrine, and ganglion cells. Glycinergic amacrine cells can be immunolabeled with antibodies against glycine or against the glycine transporter GlyT1 (13-15). Figure 2 shows a vertical section through a mouse retina that was double immunolabeled for glycine and for GlyT1 (16). Strong glycine immunoreactivity can be observed in amacrine cell bodies and their dendrites descending into the inner plexiform layer (IPL) or in dendrites from interplexiform amacrine cells ascending into the outer plexiform layer (OPL). Weak glycine expression is also found in putative ON-cone bipolar cells in the outer half of the inner nuclear layer (INL). The section was also immunolabeled for GlyT1 which labels all glycinergic amacrine cells but not bipolar cells. Bipolar cells do not express GlyT1 but they receive glycine by diffusion through electrical synapses (gap junctions) from glycinergic amacrine cells (17). In other parts of the CNS, GlyT1 has been localized to glial cells, while GlyT2 is now known to represent the presynaptic neuronal glycine transporter. Surprisingly, GlyT2 does not appear to be expressed in the mammalian retina (18).

5. Morphological types of glycinergic amacrine cells

Glycinergic amacrine cells are small-field amacrine cells with principally vertically oriented dendrites, and they comprise more than 10 different morphological types (13, 19). Most of them have small, diffuse dendritic trees and perform local circuit operations between the different sublayers of the IPL.

The most prominent and also most numerous glycinergic amacrine cell is the AII amacrine cell which transfers the light signal from rod bipolar cells into the cone pathway (20). In the inner IPL, AII cells receive direct glutamatergic input from rod bipolar cells, but they are also engaged with ON-cone bipolar cell axon terminals via electrical synapses (gap junctions). In the outer IPL. AII cell lobular dendrites provide glycinergic, chemical output synapses onto OFF-cone bipolar cell axon terminals and dendrites of OFF ganglion cells. Further glycinergic, small-field amacrine cells were identified in the cat retina by combined Golgi-staining and glycine uptake (21), and Menger et al. (13) identified at least 8 different glycinergic amacrine cells in the rat retina (Fig. 3).

Recently it became possible to study glycinergic amacrine cells in the retina of transgenic mice which express green fluorescent protein (GFP) under the control of the Thy1 promotor (Thy1-GFP-O) (22, 23). Three such cells are illustrated in figure 4, with double labeling for calcium binding protein 5 (CaBP5) in order to reveal the different sublaminas of the IPL and possible bipolar cell candidates as synaptic partners. The cells in figures 4A

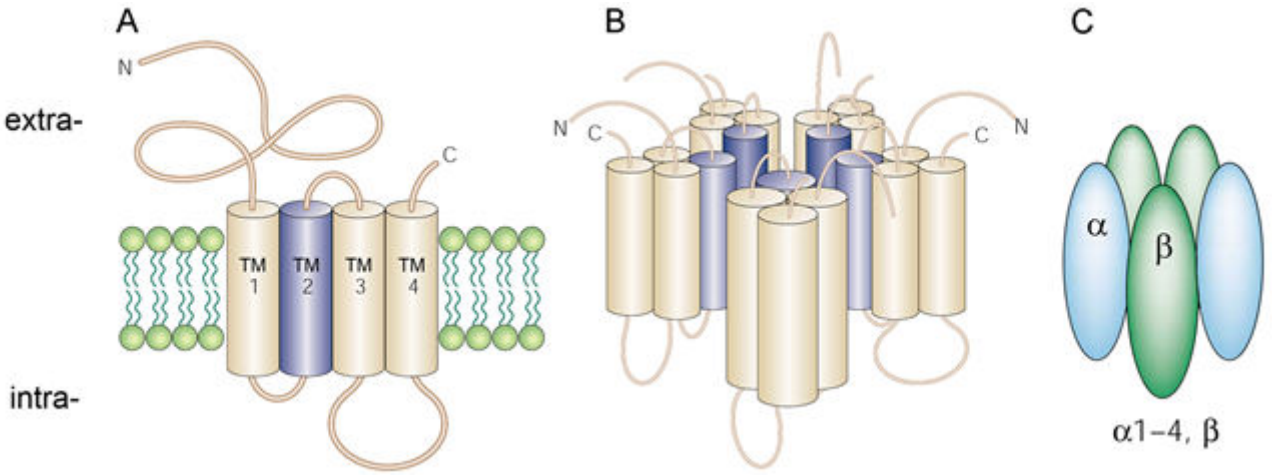

Figure 1. Structure of ligand-gated ion channels. A. Each GlyR subunit consists of a large N-terminal extracellular domain, four transmembrane segments (TM1–TM4), a long intracellular loop connecting TM3 and TM4, and a short extracellular C-terminus. B. Proposed structure of a ligand-gated ion channel. TM2 forms the lining of the ion pore. C. Glycine receptors are pentamers constructed from α and β subunits in a ratio of 2α:3β. From Moss and Smart, 2001 (54).

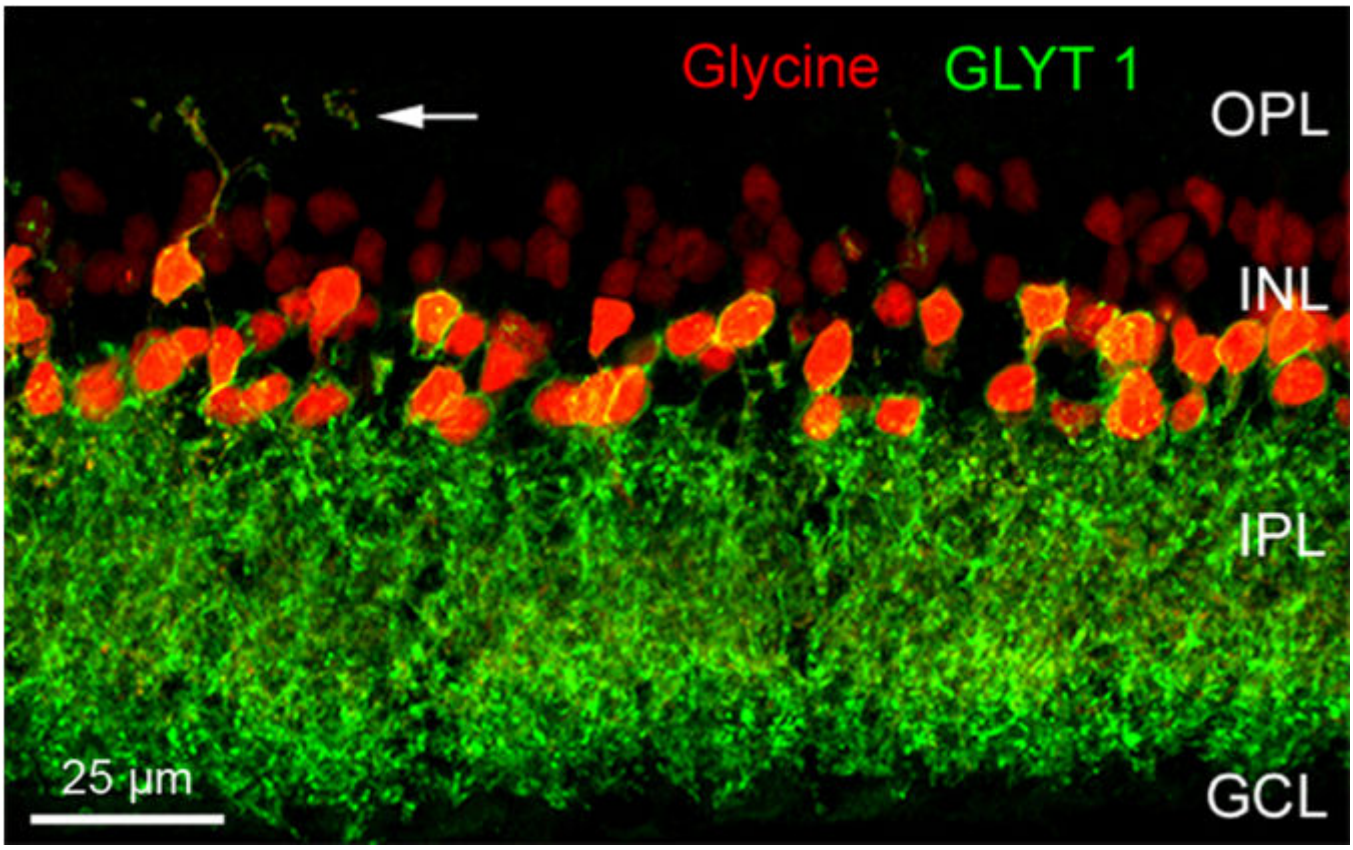

Figure 2. Glycinergic amacrine cells of the mouse retina. A vertical section was double immunolabeled for glycine (red) and the glycine transporter GlyT1 (green). The arrows indicate an interplexiform process ascending to the OPL (OPL: outer plexiform layer; INL: inner nuclear layer; IPL: inner plexiform layer; GCL; ganglion cell layer). From Haverkamp and Wässle, 2000 (16).

and B have small, diffuse dendritic trees; the cell in figure 4C has a bistratified appearance and has been identified as A8 cell in cats and human retinas (24-26) (see also chapter on 'Roles of Amacrine Cells', Webvision).

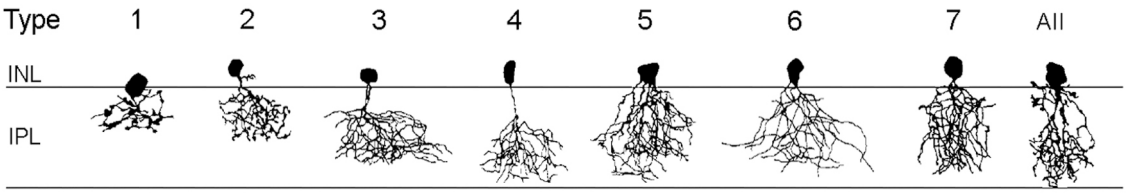

Figure 3. Glycinergic amacrine cells of the rat retina. From Menger, Pow and Wässle, 1998 (13).

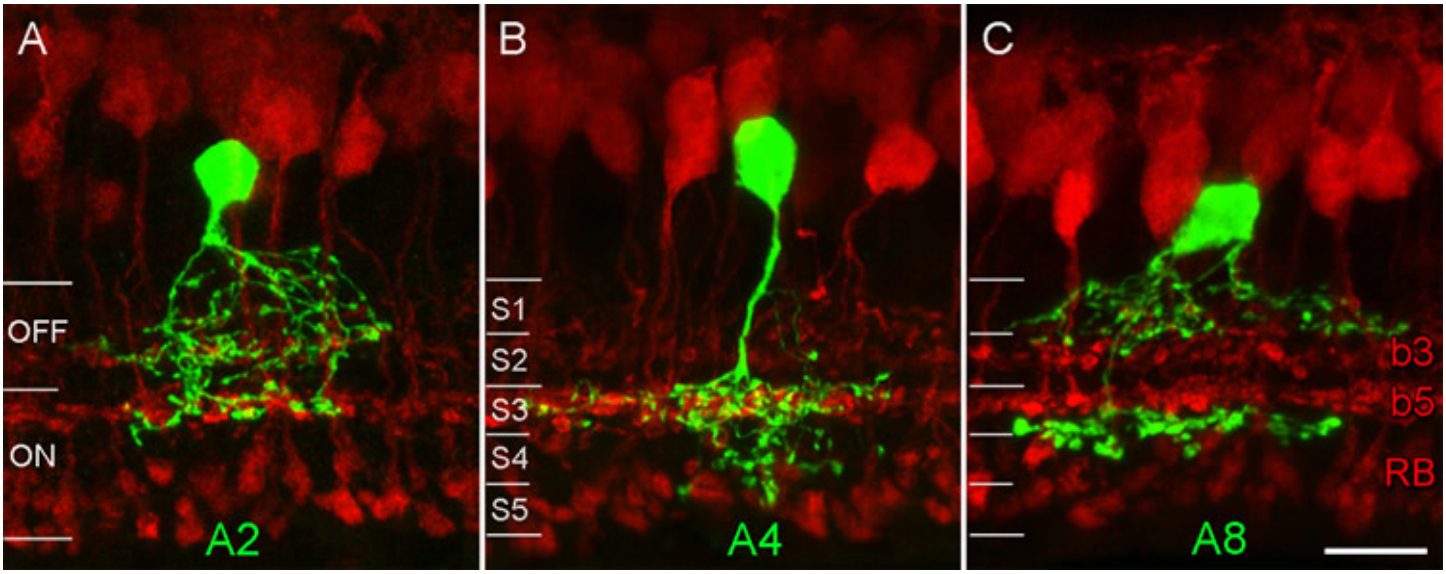

Figure 4. Glycinergic amacrine cells expressing GFP in the Thy1-GFP-O mouse. Sections are double labeled for bipolar cell marker CaBP5 (red). CaBP5 is expressed in rod bipolar cells (RB), in type 5 ON-cone bipolar cells (b5), and in type 3 OFF-cone bipolar cells (b3) (55). A2 and A4 amacrine cells are classified according to the scheme of Menger et al., 1998 (13); A8 according to Kolb et al., 1981 (26). Scale bar: 25 µm. Unpublished data.

6. GlyR diversity in the mouse retina

The diversity of types of glycinergic amacrine cells is paralleled by the striking heterogeneity of glycine receptors. All four α subunits of the GlyR have been localized to specific synapses within the mammalian retina (23, 27-30). When subunit selective antibodies were applied to lightly fixed tissue, they each produced a distinct punctate immunofluorescence pattern (Figure 5).

The GlyRα1 subunit is expressed in a sparse population of puncta in the OPL, which represent synapses between glycinergic interplexiform cells and bipolar cell dendrites (Fig. 5A). In the outer IPL (stratum S1 and S2) GlyR α1 immunoreactivity is found in large puncta, which occur at high density. They represent synapses between AII amacrine cells and OFF-cone bipolar cells (30). In the inner IPL (stratum S3-S5) smaller GlyRα1 immunoreactive puncta can be observed representing synapses onto ganglion cell dendrites and rod bipolar cell axons (31, 32). The GlyRα2 subunit is more uniformly distributed across all strata (Fig. 5B), and GlyRα2 immunoreactive puncta occur at the highest density amongst the four α subunits (28). The GlyRα3 subunit (Fig. 5C) shows four bands whose density of puncta successively declines towards the ON sublamina (27). Lastly, the GlyRα4 subunit (Fig. 5D) shows a band of high density of puncta at the border between stratum 3 and 4 and further small and sparsely distributed puncta throughout the remaining strata (23). Taken together, the characteristic distribution of subunits across the IPL suggests that the GlyR subtypes are expressed at different synapses and are involved with different neuronal circuits.

Electron microscopy confirms the notion that the immunofluorescent puncta represent clusters of GlyRs at postsynaptic sites. Antibodies against the α1 subunit recognize extracellular epitopes of the receptor. Thus, staining from preembedding immunoelectron-microscopic experiments appears in the synaptic cleft of the synapse (Fig. 6A). Accordingly, postembedding immunoelectron microscopy showed that the α3 subunit was localized at the postsynaptic membrane (Fig. 6B).

7. Co-localization of GlyR subunits at postsynaptic sites

Since synaptic GlyRs are composed of 2α and 3β subunits (8) there is the possibility that two different α subunits co-exist in a single heteromeric GlyR. In addition, it is possible that two different GlyR subtypes, such as α2β and α3β GlyRs co-distribute at the same postsynaptic sites. In both cases, the immunoreactive hot spots should coincide. However, when retinal sections were double labeled for the GlyRα1 subunit and the other three GlyRα subunits, no statistically significant coincidence rate of immunoreactive puncta was observed. When retinal sections were double labeled for the GlyRα2 and α3 subunits a coincidence rate of 26.7% was found (28). In retinal sections double labeled for the GlyRα3 and α4 subunits no significant coincidence rate was found (23). In sections double labeled for the GlyRα4 and α2 subunits, 31.5% of the α4 immunoreactive clusters also contained the α2 subunit (Fig. 7). The results indicate that postsynaptic GlyR clusters usually contain only one type of α subunit. The exception is approximately one third of synapses immunoreactive for GlyR α2 which can also contain the α3 or the α4 subunits.

8. Expression of GlyRs by identified neurons

In order to reveal the involvement of selected GlyR subtypes with different retinal circuits, identified neurons were immunostained for the different GlyR α subunits. Figure 8 shows a GFP labeled A-type ganglion cell in a whole mount of Thy1-GFP-O mouse retina (32). The retina was immunolabeled for the GlyRα1 subunit demonstrating that many GlyRα1 immunoreactive puncta decorate the dendrites of this A-type ON ganglion cell. A coincidence of puncta and dendrites was also obvious for A-type OFF ganglion cells, which suggests that both ON and OFF A-type ganglion cells receive glycinergic input through α1 subunit expressing synapses. A-type ganglion cells were also double labeled for the other α subunits but quantification showed that the predominant input is through GlyRα1 containing synapses (32).

Figure 9 shows a vertical view of a Type 3 glycinergic amacrine cell in the Thy1-GFP-O mouse retina (33). Many GlyRα2 immunoreactive puncta (red) coincide with dendritic varicosities of the Type 3 cell (green) (Fig. 9D-F). Since this cell is a glycinergic amacrine cell, the puncta may represent input synapses the cell receives from other glycinergic amacrine cells or output synapses the cell makes onto other, non-labeled neurons. The fact that the red GlyRα2 immunoreactive puncta are always slightly displaced from the green varicosities (Fig. 9F) indicates that these synaptic GlyRα2 clusters are expressed by unknown neurons that are postsynaptic to this Type 3 cell.

The two examples of cells presented in figure 8 and figure 9 suggest a correlation between the morphological type of a given neuron and the molecular signature of the glycinergic synapse it receives or forms onto postsynaptic neurons. In this context one interesting question is whether the presynaptic neuron instructs the postsynaptic cell to express certain GlyR subunits or whether a given postsynaptic neuron expresses an exclusive GlyR subtype. To address this question a detailed physiological characterization of selected synaptic GlyRs on individual cells is essential.

To date, selective agonists or antagonists that distinguish different isoforms of synaptic GlyRs have not been identified (1, 34). However, mutant mice are available that have dysfunction of specific GlyR subunits and thus it became possible to study details of the glycinergic synaptic transmission in the mammalian retina (31, 32, 35, 36). The kinetic properties of GlyRs were measured by recording spontaneous inhibitory postsynaptic currents (sIPSCs) from identified retinal neurons in wild-type mice and mice lacking GlyR α subunit (*Glra1*$^{spd\text{-}ot}$, *Glra2*

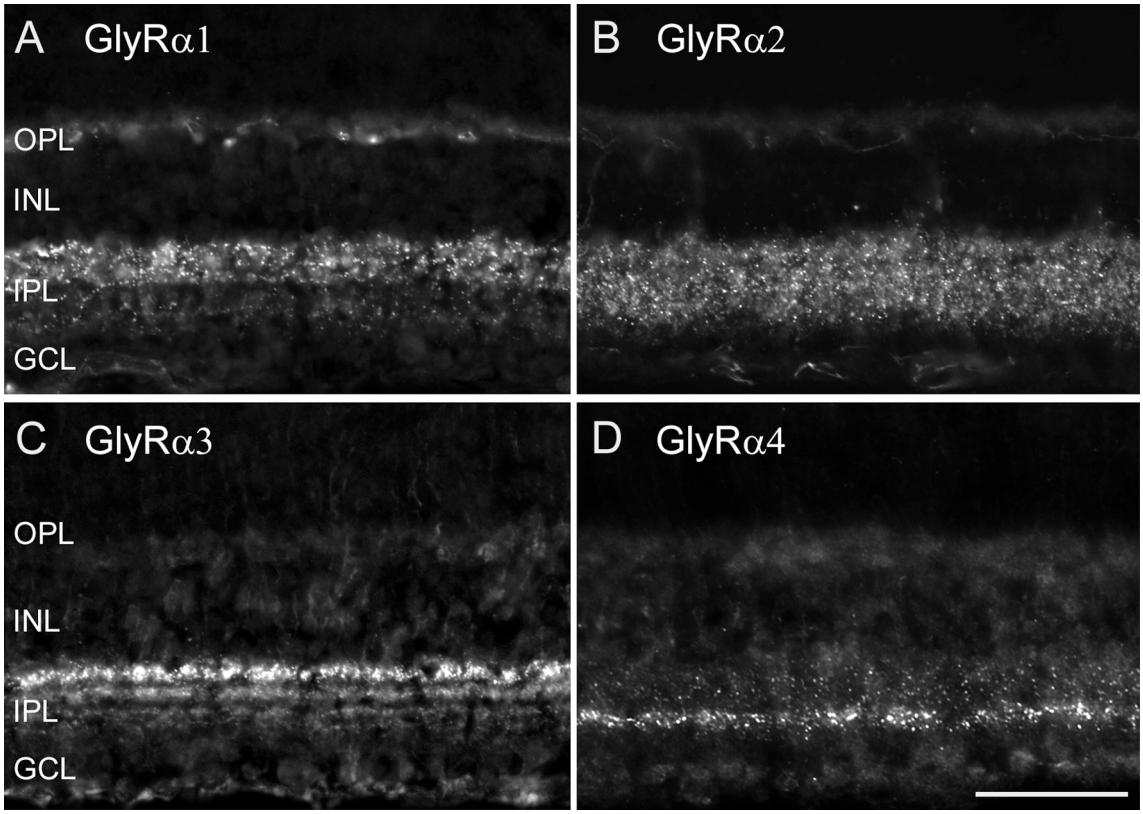

Figure 5. Diversity of GlyR subtypes in the mouse retina. A. GlyRα1 immunoreactive puncta are most prominent in the outer IPL (OFF sublamina). B. GlyRα2 immunofluorescence is more evenly distributed across the IPL. C. GlyRα3 expression is found in four bands. D. GlyRα4 is most prominent in a small band at sublamina 3/4 border. Scale bar: 50 µm. From Heinze et al., 2007 (23).

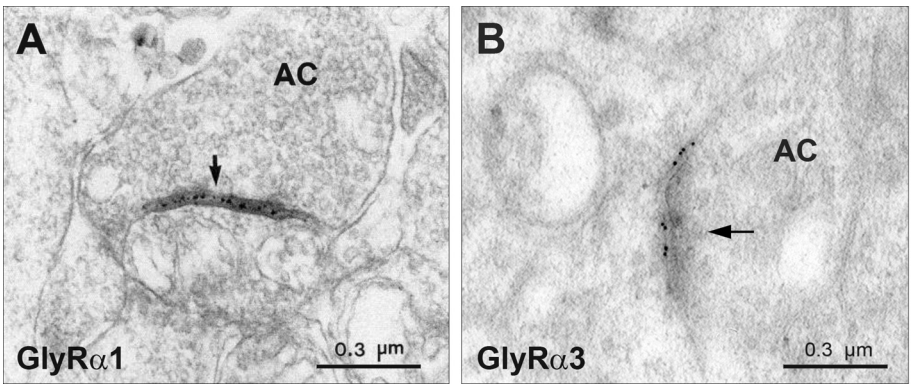

Figure 6. Synaptic localization of two GlyR subunits at conventional synapses in the IPL. A. Preembedding electron microscopy on vibratome sections of rat retina. The figure shows an amacrine cell synapse (AC, arrow) with GlyRα1 immunoreactivity. From Sassoè-Pognetto et al., 1994 (30). B. Postembedding electron microscopy of GlyRα3 on ultrathin sections of mouse retina. The GlyR subunit is localized at the postsynaptic membrane of an amacrine cell synapse (provided by Christian Puller, unpublished data).

and *Glra3*. From the observed differences of sIPSCs in wild-type and mutant mice, the cell-type specific subunit composition of GlyRs can be defined.

Glycine receptors expressed by bipolar cells

Patch-clamp recordings performed from identified bipolar cells in slices of the mouse retina (31) enabled the study of GlyRs by the application of exogenous glycine and by recording glycinergic spontaneous inhibitory

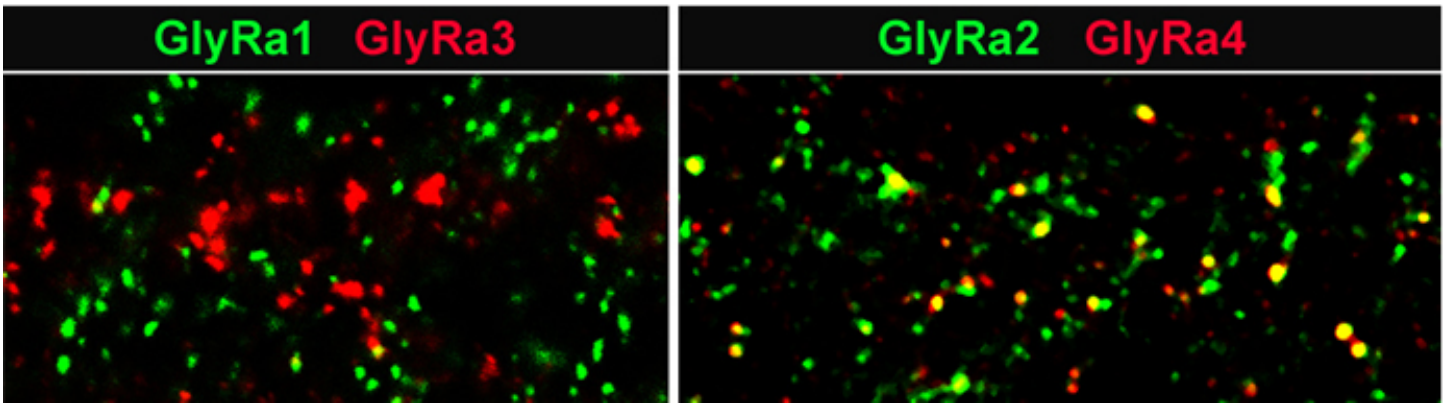

Figure 7. Colocalization of GlyR subunits at postsynaptic sites. GlyRα3 and GlyRα1 immunoreactive puncta are not colocalized whereas GlyRα2 and GlyRα4 immunoreactive puncta sometimes colocalize. From Haverkamp et al., 2003 (27); Heinze et al., 2007 (23).

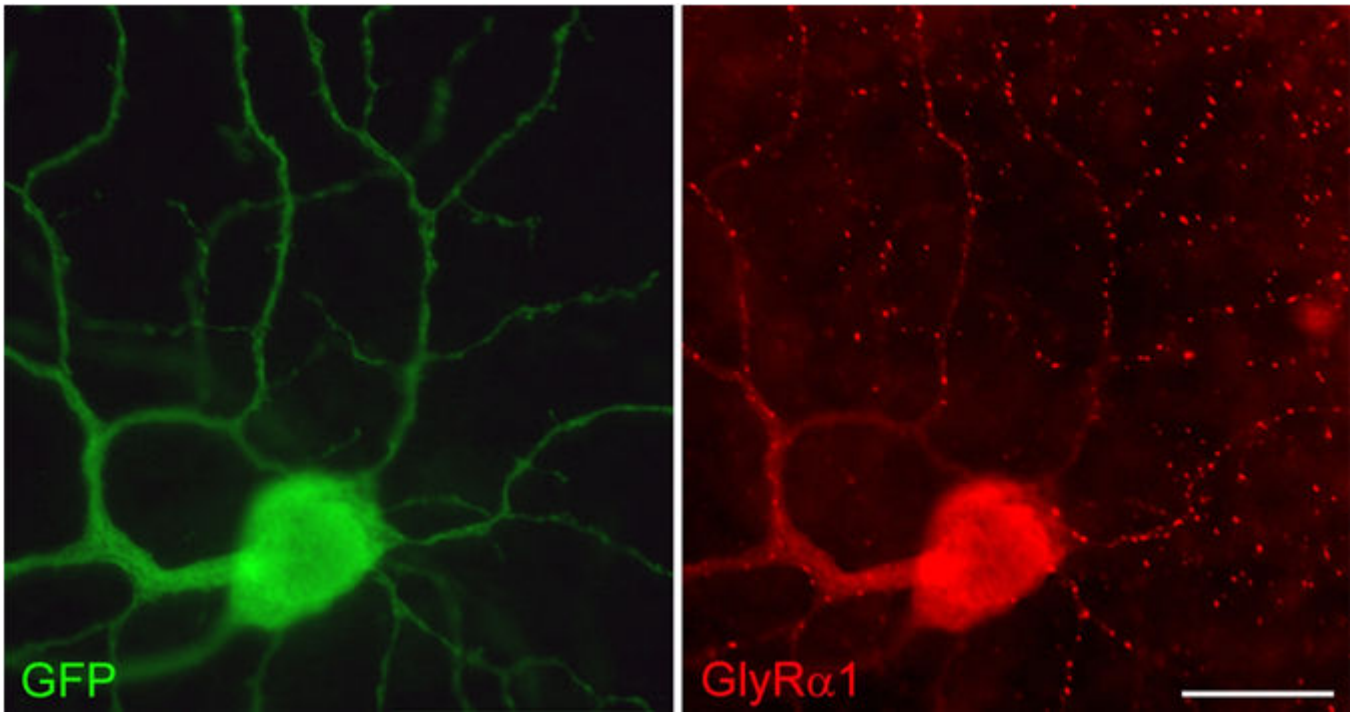

Figure 8. Colocalization of GlyRα1 with the dendrites of an A-type ganglion cell. The image on the left shows an A2-ON ganglion cell in the Thy1-GFP-O mouse (22). The whole mount was also immunostained for GlyRα1 and many immunoreactive puncta decorate the dendrites of this ganglion cell. Scale bar: 20 μm. From Majumdar et al., 2007 (32).

postsynaptic currents (sIPSCs). Glycine application elicited large-amplitude currents in all OFF-cone and rod bipolar cells while ON-cone bipolar cells exhibited only very small, if any, glycinergic currents (Fig. 10 (31, 37),). By comparing sIPSCs of bipolar cells in wild-type and *Glra3*$^{-/-}$ mice, no statistically significant differences were found; whereas glycine-induced currents and sIPSCs were absent from all bipolar cells of *Glra1*$^{spd\text{-}ot}$ mice. Thus, OFF-cone and rod bipolar cells receive kinetically fast glycinergic inputs, preferentially mediated by GlyRs composed of α1 and β subunits (decay time constant $\tau \sim 5$ ms). Slow sIPSCs, the characteristic of GlyRs containing the α2 subunit, were not observed in bipolar cells.

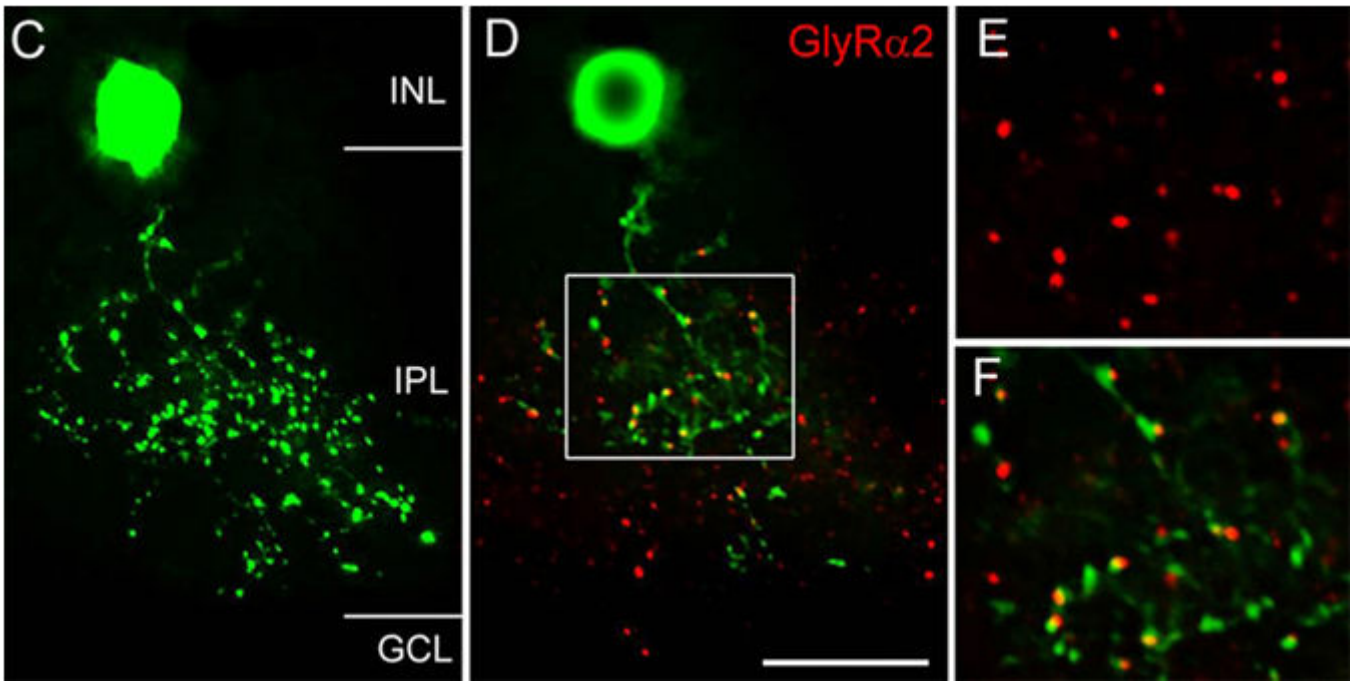

Figure 9. Association of GlyRα2 with a glycinergic amacrine cell. C. Type 3 amacrine cell from the Thy1-GFP-O mouse retina. D. Single confocal section of the cell in C also immunostained for GlyRα2. The boxed area is shown at higher magnification in E and F. Scale bar: 17 µm in C & D, 10 µm in E & F. From Wässle et al., 2009 (33).

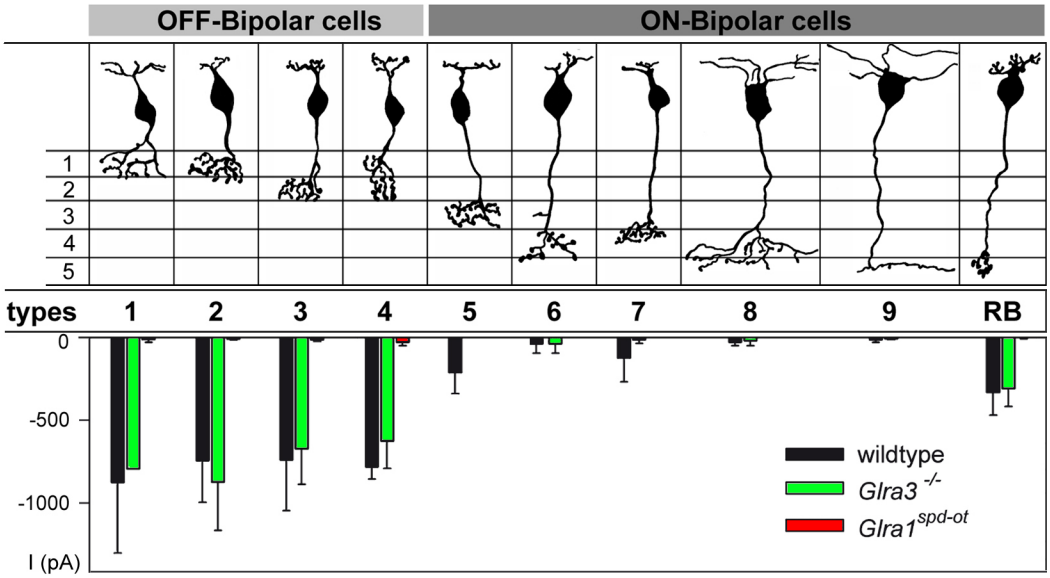

Figure 10. Glycine-induced currents from mouse bipolar cells. OFF- and ON-bipolar cells of the mouse retina as described by Ghosh et al., 2004 (55) and summary diagram of the peak amplitudes of inward currents elicited by the application of glycine (1–2 mM) in the nine cone bipolar cell types and rod bipolar (RB) cells of wild-type, Glra3$^{-/-}$ and Glra1$^{spd\text{-}ot}$ mice. From Ivanova et al., 2006 (31).

Glycine receptors on AII and narrow-field amacrine cells

Amacrine cells are known to express strychnine-sensitive glycine receptors. The GlyRs expressed by AII amacrine cells and by the narrow-field (NF) amacrine cells (Fig. 11A) were studied by patch-clamp recordings in mouse retinal slices (36). Glycinergic sIPSCs of AII cells displayed medium fast kinetics (τ ~ 11 ms, Fig. 11B), which were completely absent in the *Glra3*$^{-/-}$ mouse, indicating that synaptic GlyRs of AII cells mainly contain

the α3 subunit. Glycinergic sIPSCs of NF cells had slow kinetics (τ ~ 27 ms, Figs. 11B and 12C) that were significantly prolonged in *Glra2*$^{-/-}$ mice (τ ~ 69 ms, Fig. 12F). These data show that morphologically distinct amacrine cells express different sets of glycine receptors.

Glycine receptors expressed by wide-field amacrine cells

Glycine induced currents and sIPSCs were also recorded from displaced wide-field, putative GABAergic amacrine cells. These GlyRs had slow kinetics (τ ~ 25 ms) (35, 38) comparable to NF amacrine cells. ON-starburst (cholinergic amacrine cells) had sIPSCs with extremely long decay time constants (τ ~ 50 - 70 ms), which did not differ between wild-type and the three mutant mice (35). Since GlyR α4 immunoreactive puncta (Fig. 5D) occur at higher density along the dendrites of ON-starburst amacrine cells, it is possible that GlyRs of ON-starburst cells are dominated by the α4 subunit. This would in turn suggest that GlyRs containing the α4 subunit have slow kinetics.

Glycine receptors expressed by ganglion cells

There are more than ten different types of ganglion cells in any mammalian retina. The GlyRs expressed by A-type ganglion cells (alpha-cell homologues) of the mouse retina were also investigated both in wild-type and mutant mice (32). In the wild-type retina, glycinergic sIPSCs of A-type ganglion cells have fast kinetics (mean τ = 3.9 ± 2.5 ms). Glycinergic sIPSCs recorded from *Glra2*$^{-/-}$ and *Glra3*$^{-/-}$ mice did not differ from those of wild-type mice. However, the number of glycinergic sIPSCs was significantly reduced in *Glra1*$^{spd\text{-}ot}$ mice and the remaining sIPSCs had slower kinetics. These results show that A-type ganglion cells receive preferentially kinetically fast glycinergic inputs, mediated by GlyRs containing the α1 subunit.

B-type cells (beta-cell homologues) are probably involved with sustained neurotransmission. They are also believed to perform complex tasks like local edge detection. However, the specific roles of different B-type cells in the mouse retina are not yet clearly understood. There are four classes of small-field B-type ganglion cells (39), and there seems to be a substantial heterogeneity with respect to GlyR expression in these cell types. GlyRs of B1 cells are dominated by the α1 subunit, while in B4 cells the α3 subunit plays an important role. B2 and B3 cells express a more balanced mixture of fast (α1) and slow (α2, α3, α4) GlyR subunits (40).

9. Summary and conclusion

All four GlyR α subunits are clustered in synaptic hot spots (Fig. 5) that show characteristic distributions across the IPL of the mouse retina (23). Gephyrin is responsible for clustering GlyRs to postsynaptic sites by linking the GlyR β subunit to the cytoskeleton (5, 41). No GlyR clusters could be detected in gephyrin deficient mouse retinas (42), which suggests that synaptic GlyRs in the retina are always heteromeric. In the adult, two copies of the α subunit and three copies of the β subunit form the pentameric receptor protein (8).

Bipolar cells and A-type ganglion cells represent the fast transfer channel of the mammalian retina and, therefore, express α1β GlyRs with fast kinetics. AII amacrine cells relay rod light signals with lower temporal resolution and express α3β GlyRs with medium-fast kinetics. NF amacrine cells are modulatory interneurons, where temporal precision seems less important and they express the α2β and α4β GlyRs with slow kinetics.

Both GABA and glycine inhibition are used to modulate different aspects of ganglion cell responses and receptive field (RF) organization (43-45). GABAergic amacrine cells often provide feedforward inhibition and target both $GABA_A$Rs and $GABA_C$Rs in reciprocal inhibitory circuits to modulate the RF center excitation (46), and they target $GABA_A$Rs to amplify and refine the RF surround (47). Glycinergic inhibition on the other hand modulates less spatial than temporal properties and may increase the gain of the ganglion cell response. Glycinergic amacrine cells often use (crossover) inhibition to modulate ganglion cell excitatory inputs within their RF center (48-52).

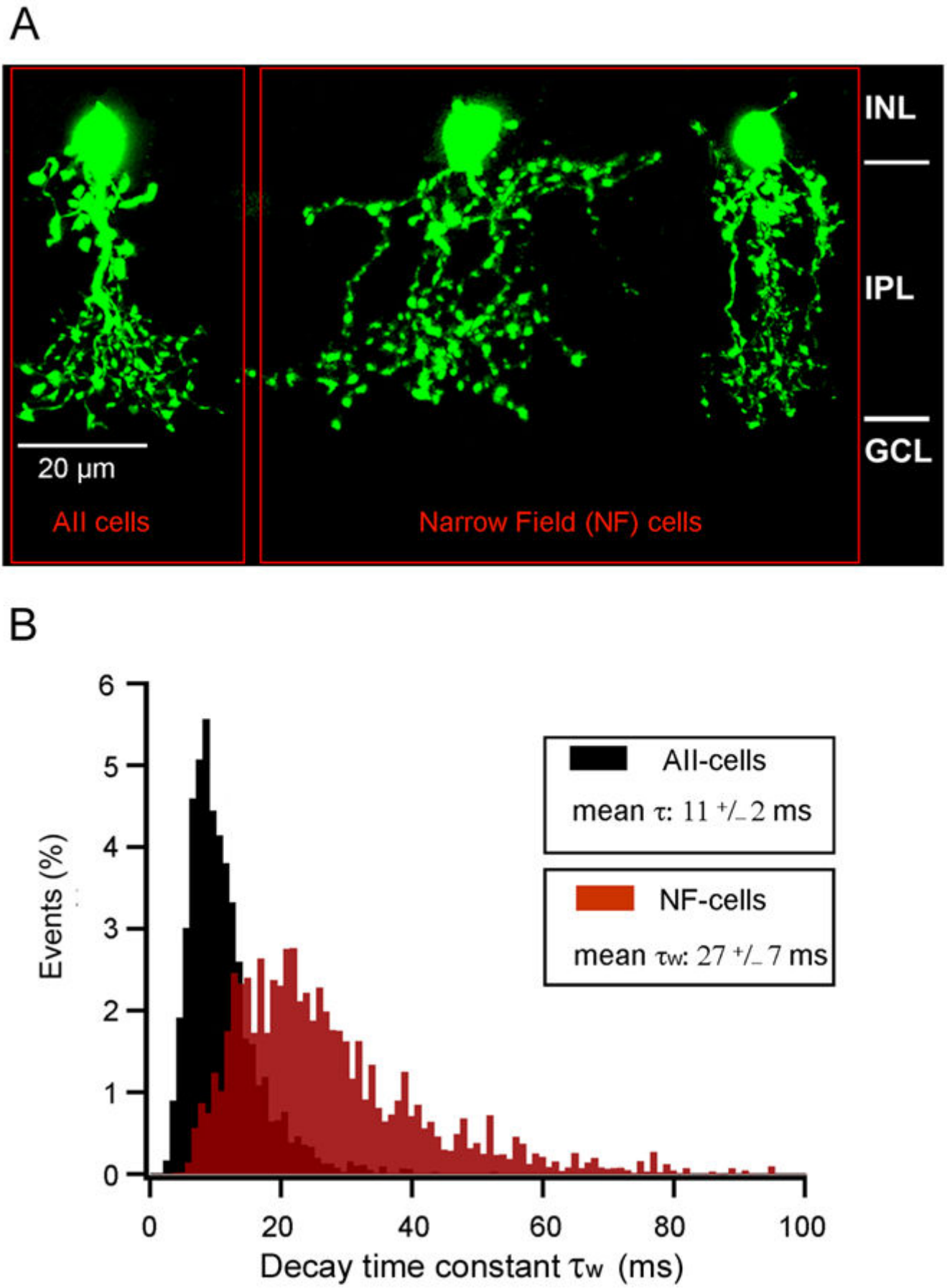

Figure 11. Glycinergic sIPSCs of mouse narrow-field amacrine cells. A. Examples of recorded AII, and narrow field (NF) glycinergic amacrine cells. B. Frequency histogram of decay time constants of glycinergic sIPSCs recorded from AII cells and from NF cells in

wild-type mice. From Weiss et al., 2008 (36).

About the Authors

Silke Haverkamp received her PhD from the Carl von Ossietzky Universität Oldenburg, Germany, in Visual Neuroscience under the mentorship of Josef Ammermüller. She was a postdoctoral researcher at the Boston University with Bill Eldred and then at the Moran Eye Center in Salt Lake City with Helga Kolb. Afterwards, Silke moved back to Germany to join the Department of Neuroanatomy headed by Heinz Wässle at the Max Planck Institute of Brain Research in Frankfurt. She has now her own research group at the Institute and focuses on the structure and function of neurons and synaptic circuits within the mammalian retina, using neuroanatomical and electrophysiological methods.

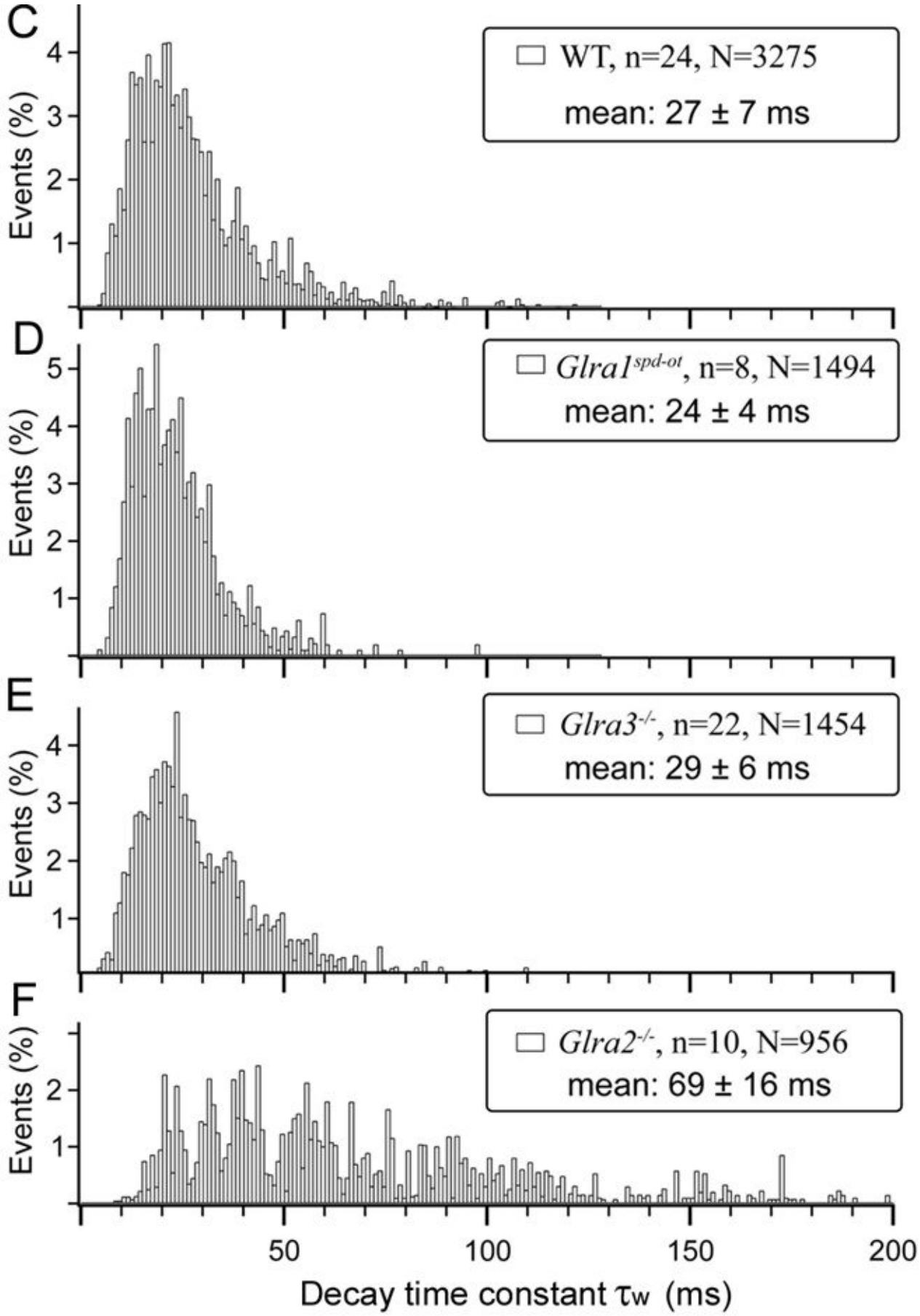

Figure 12. Mutations of glycine receptor α subunits change sIPSC decay times. C-F. Decay time constants of glycinergic sIPSCs

recorded from narrow field (NF) cells of wild-type, *Glra*$^{spd\text{-}ot}$, *Glra3*$^{-/-}$ and *Glra2*$^{-/-}$ mice. From Weiss et al., 2008 (36).

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