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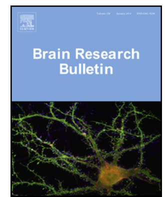

Research report

Gephyrin and the regulation of synaptic strength and dynamics at glycinergic inhibitory synapses

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ABSTRACT

Glycinergic synapses predominate in brainstem and spinal cord where they modulate motor and sensory processing. Their postsynaptic mechanisms have been considered rather simple because they lack a large variety of glycine receptor isoforms and have relatively simple postsynaptic densities at the ultrastructural level. However, this simplicity is misleading being their postsynaptic regions regulated by a variety of complex mechanisms controlling the efficacy of synaptic inhibition. Early studies suggested that glycinergic inhibitory strength and dynamics depend largely on structural features rather than on molecular complexity. These include regulation of the number of postsynaptic glycine receptors, their localization and the amount of co-localized $GABA_A$ receptors and GABA-glycine co-transmission. These properties we now know are under the control of gephyrin. Gephyrin is the first postsynaptic scaffolding protein ever discovered and it was recently found to display a large degree of variation and regulation by splice variants, posttranslational modifications, intracellular trafficking and interactions with the underlying cytoskeleton. Many of these mechanisms are governed by converging excitatory activity and regulate gephyrin oligomerization and receptor binding, the architecture of the postsynaptic density (and by extension the whole synaptic complex), receptor retention and stability. These newly uncovered molecular mechanisms define the size and number of gephyrin postsynaptic regions and the numbers and proportions of glycine and $GABA_A$ receptors contained within. All together, they control the emergence of glycinergic synapses of different strength and temporal properties to best match the excitatory drive received by each individual neuron or local dendritic compartment.

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1. Introduction

Glycinergic neurotransmission is most important in the inhibitory networks of the spinal cord, brainstem and retina, while GABAergic neurotransmission predominates in the forebrain. Glycinergic synapses operate through glycine-gated chloride channel-receptors (GlyR) with ion permeabilities similar to $GABA_A$ receptors, but different conductance levels (Bormann et al., 1987; Smith et al., 1989). Importantly, glycinergic synaptic currents are usually of larger peak amplitudes and faster kinetics than those mediated by $GABA_A$ receptors (Gonzalez-Forero et al., 2005; Gonzalez-Forero and Alvarez, 2005; Jonas et al., 1998; Legendre, 2001; Takahashi et al., 1992), and perhaps better tuned to the synaptic integrative properties of spinal and brainstem neurons involved in motor control and sensory processing. Mutations affecting glycinergic neurotransmission are therefore tightly associated with motor problems and startle disease (Harvey et al., 2008; Schaefer et al., 2013), but they are also related to chronic pain (Lynch and Callister, 2006) and deficits in auditory processing (Wang et al., 2011).

The goal of this review is to highlight the central role of gephyrin (from the Greek γεφηρα: "bridge"; Prior et al., 1992) in glycinergic synapse structure and function. Gephyrin is a protein of the postsynaptic density at inhibitory synapses that when first discovered it was proposed to serve as a GlyR anchoring protein (Pfeiffer et al., 1982; Triller et al., 1985), but thereafter it was found to encompass a large diversity of isoforms and posttranslational modifications that influence the size and density of postsynaptic receptor clusters and differentially modulate receptor recruitment and stability of not only GlyRs but also $GABA_A$ receptors, thereby controlling important aspects of glycinergic synapse function like the amplitude and

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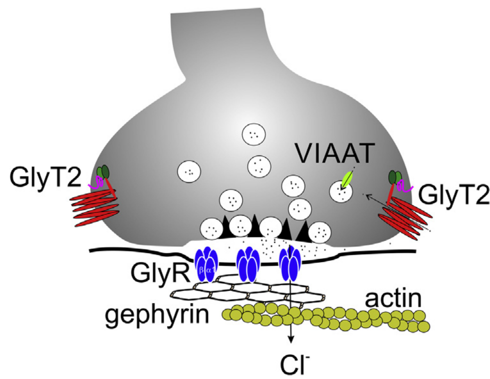

Fig. 1. Basic organization of a glycinergic synapapse. Glycine accumulated in the axopalms through the activity of the GlyT2 glycine transporter and form this cytosolic pools is accumaulated inside vesicle by the vesicular inhibitory aminoacid transporter (VIAAT). Release glycine postsynaptic glycine receptor (GlyR) than when open they pass mainly chloride (Cl-) according to it electrochemical gradient (in- mature neurons = hyperpolarizing; out-immature neurons = depolarizing). Postsynaptic GlyRs in mature neurons are mostly α1β subunit composition and are anchored postsynaptically by gephyrin to the submembrane actin cystoskeleton.

time course of the postsynaptic currents. In the initial sections of this review the functional significance of gephyrin postsynaptic clustering and its matching to convergent excitatory inputs will be considered. Later the molecular basis of gephyrin regulation and postsynaptic receptor recruitment and their modulation by synaptic activity will be discussed.

2. Basic organization of glycinergic synapses

Glycinergic synapses (Fig. 1) lack the molecular complexity of $GABA_A$ synapses. Glycinergic synapses do not express the variety of presynaptic neurotransmitter synthesizing enzyme isoforms characteristic of GABAergic synapses and that finely modulate neurotransmitter synthesis and release. Glycinergic synapses neither display a large variety of postsynaptic receptor subunit compositions, similar to the $GABA_A$ receptor conferring different properties to GABAergic neurotransmission in different brain regions. At glycinergic synapses, glycine accumulates inside synaptic vesicles from a high cytosolic glycine concentration set predominantly by uptake from the extracellular space by plasma membrane glycine transporters, specifically the isoform 2 or GlyT2 (Gomeza et al., 2003; Latal et al., 2010; Rousseau et al., 2008). Lack of GlyT2 causes a dramatic reduction in glycinergic neurotransmission that is not compensated by metabolic glycine production or upregulation of GABA neurotransmission (Latal et al., 2010). Thus, GlyT2 knockout animals display a profound motor phenotype and die in the second postnatal week (Gomeza et al., 2003). Glycine is loaded into synaptic vesicles through the vesicular inhibitory aminoacid transporter (VIAAT) that is shared with GABA (Wojcik et al., 2006). Upon synaptic release, glycine interacts with postsynaptic GlyRs that, in the adult, are usually heteromeric pentamers composed by α1 and β subunits with stoichiometry 3α:2β or 2α:3β (Dutertre et al., 2012; Legendre, 2001; Lynch, 2009). Glycine binds to the α subunit and double binding is necessary for GlyR openings that have characteristic short mean open times (Legendre, 2001; Takahashi et al., 1992) and result in the brief time courses of glycinergic synaptic currents. The genes for one type of β subunit and 4 α subunits have been identified and different subunit compositions display different kinetics and ligand affinities (Zhang et al., 2015). Further heterogeneity arises from splice variants, posttranslational modifications and the fact that some GlyRs are pentameric homomers of α subunits. However, GlyRs other than α1β heteromers have their expression restricted to development (i.e., α2 homomers) or limited distributions (i.e., α2β and α3β containing GlyRs are mostly found in retina, superficial spinal cord dorsal horn and cerebellum). More complete descriptions on the molecular biology, distribution and pharmacology of GlyRs can be found in other reviews (Dutertre et al., 2012; Legendre, 2001; Lynch, 2009). Compared to the variety of molecular organizations in the pre and postsynaptic elements of glutamatergic and GABAergic synapses, glycinergic synapses in the adult have fewer molecular variants that modulate neurotransmitter content presynaptically and fewer GlyR subunit combinations to influence ligand binding, channel kinetics and pharmacology, postsynaptically.

Glycinergic synapses nonetheless modify their function and synaptic strength by controlling, among others, three important variables: 1) the number of glycine postsynaptic receptors; 2) the localization of synapses in cell body, proximal or distal dendrites; 3) GABA co-transmission. All three features are regulated by gephyrin-dependent mechanisms, highlighting the importance of gephyrin as a central controller of glycinergic synapse structure and function. This review will focus on activity-dependent mechanisms of gephyrin regulation that modulate glycinergic synapse strength. More complete reviews on gephyrin molecular biology and its role in GABAergic synapses can be found elsewhere (Choii and Ko, 2015; Fritschy et al., 2008; Tretter et al., 2012; Tyagarajan and Fritschy, 2014; Zacchi et al., 2014).

3. Diversity of gephyrin clustering and inhibitory glycinergic synapse organization

Using gephyrin as a marker of the postsynaptic density of inhibitory synapses it was found that in the spinal cord *in vivo*, neurons display cell-type specific organizations of gephyrin clustering such that for most neurons, including α and γ-motoneurons, inhibitory synapses are distributed throughout the cell body and dendrites with structural variations in gephyrin postsynaptic densities that depend on synapse location (Alvarez et al., 1997). Proximal inhibitory synapses are opposed by 4–15 individual gephyrin rounded spots that are rather small (<0.1–0.2 μm^2) and organized in "rosettes" (Fig. 2A). The lower boundaries of their size distribution was initially ambiguous because the diffraction limit in resolving power of wide-field and confocal microscopy, but using superresolution techniques it was recently estimated that small clusters in spinal cord neurons average around 0.06 μm^2 in size (Specht et al., 2013). In contrast, gephyrin patches coalesce in the distal dendrites where they form fewer clusters, but of larger size (from 0.2 to more than 1 μm^2) and variable morphologies. This sets a somatodendritic gradient in which proximal inhibitory synapses are opposed by several small, circular and independent gephyrin clusters, while synapses on the distal dendrites are opposed by fewer more pleomorphic larger patches. A similar organization was observed in the Mauthner cell of the teleost fish brainstem (Triller et al., 1990). One exception to this somatodendritic gradient in the mammalian spinal cord is a class of spinal interneuron that provides feedback inhibition to motoneurons and is known as the Renshaw cell (Eccles et al., 1954; Renshaw, 1946). Renshaw cells lack gephyrin and inhibitory synapses in their distal dendrites, but their cell body and proximal dendrites are covered by a high density of inhibitory synapses (>90% of the total synaptic coverage on the cell bodies, Alvarez F.J., unpublished results) with extraordinarily large postsynaptic gephyrin patches, some larger than 3.5 μm^2 (Alvarez et al., 1997; Geiman et al., 2000) (Fig. 2A). In all cases the glycinergic nature of gephyrin-labeled inhibitory synapses was confirmed by co-labeling for GlyR subunits and the distribution of postsynaptic GlyRs was co-extensive with the gephyrin clustering area. Gephyrin is also an organizer of postsynaptic densities in forebrain inhibitory synapses, but in this case the synapses are purely GABAergic, lacking GlyRs. Although GABAergic synapses also dis-

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