Progress in Neurobiology 91 (2010) 349–361

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Glycine and glycine receptor signaling in hippocampal neurons: Diversity, function and regulation

Tian-Le Xu *, Neng Gong

Institute of Neuroscience and State Key Laboratory of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 320 Yue-yang Road, Shanghai 200031, China

ARTICLE INFO

Article history:
Received 5 January 2010
Received in revised form 20 April 2010
Accepted 27 April 2010

Keywords:
Glycine
Glycine receptor
NMDA receptor
Hippocampus
Homeostatic regulation

ABSTRACT

Glycine is a primary inhibitory neurotransmitter in the spinal cord and brainstem. It acts at glycine receptor (GlyR)-chloride channels, as well as a co-agonist of NMDA receptors (NMDARs). In the hippocampus, the study of GlyRs has largely been under-appreciated due to the apparent absence of glycinergic synaptic transmission. Emerging evidence has shown the presence of extrasynaptic GlyRs in the hippocampus, which exert a tonic inhibitory role, and can be highly regulated under many pathophysiological conditions. On the other hand, besides D-serine, glycine has also been shown to modulate NMDAR function in the hippocampus. The simultaneous activation of excitatory NMDARs and inhibitory GlyRs may provide a homeostatic regulation of hippocampal network function. Furthermore, glycine can regulate hippocampal neuronal activity through GlyR-mediated cross-inhibition of GABAergic inhibition, or through the glycine binding site-dependent internalization of NMDARs. Therefore, hippocampal glycine and its receptors may operate in concert to finely regulate hippocampus-dependent high brain function such as learning and memory. Finally, dysfunction of hippocampal glycine signaling is associated with neuropsychiatric disorders. We speculate that further studies of hippocampal glycine-mediated regulation may help develop novel glycine-based approaches for therapeutic developments.

© 2010 Elsevier Ltd. All rights reserved.

Contents

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, AMPA receptor; DAAO, D-amino acid oxidase; E/I, excitation–inhibition; EPSP, excitatory postsynaptic potential; FAC, fluoroacetate; GABA, γ-aminobutyric acid; $GABA_AR$, $GABA_A$ receptor; GCS, glycine cleavage system; GlyR, glycine receptor; GlyT, glycine transporter; IPSC, inhibitory postsynaptic current; KCC2, K^+-Cl^- cotransporter 2; LTD, long-term depression; LTP, long-term potentiation; mIPSC, miniature IPSC; NKCC1, Na^+-K^+-Cl^- cotransporter 1; NMDA, N-methyl-D-aspartic acid; NMDAR, NMDA receptor; PGE_2, prostaglandin E_2; PKA, protein kinase A; PKC, protein kinase C; PPR, paired-pulse ratio; PS, population spike; PSCs, postsynaptic currents; PTK, protein tyrosine kinase; RDE, rate-dependent efficacy; SHMT, serine hydroxymethyltransferase; SNAREs, soluble Nethylmaleimide-sensitive factor attachment protein receptors.

* Corresponding author. Tel.: +86 21 54921751; fax: +86 21 54921735.
E-mail address: tlxu@ion.ac.cn (T.-L. Xu).

0301-0082/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2010.04.008

1. Introduction

Glycine is a major inhibitory neurotransmitter in the spinal cord and brain stem, acting at strychnine-sensitive glycine receptor (GlyR)-chloride (Cl^-) channels (Legendre, 2001). In the hippocampus, the study of GlyRs has been largely ignored due to the apparent absence of glycinergic synaptic transmission. However, accumulating evidence shows the presence of non-synaptic GlyRs containing at least the α2 subunit in the hippocampus (Becker et al., 1993; Chattipakorn and McMahon, 2002; Malosio et al., 1991; Racca et al., 1998; Sato et al., 1992; Thio et al., 2003). Consistently, recent studies have revealed a GlyR-mediated tonic inhibition of hippocampal neuronal activity (Keck and White, 2009; Mori et al., 2002; Wang and Xu, 2006; Zhang et al., 2008a).

High brain function such as learning and memory depends critically on the balanced regulation between neuronal excitation and inhibition. As a classical inhibitory neurotransmitter, glycine is unique in that it can act as an agonist of both the inhibitory GlyRs and the excitatory NMDA receptors (NMDARs). Hippocampal glycine has been shown to simultaneously increase GlyR-mediated inhibition and facilitate NMDAR-dependent plasticity in excitatory synapses (Zhang et al., 2008a), thereby providing a potential mechanism underlying balanced regulation between excitation and inhibition in hippocampal networks. Furthermore, glycine can regulate hippocampal inhibition through GlyR-mediated down-regulation of another major inhibitory receptor, the $GABA_A$ receptors ($GABA_A$Rs) (Li and Xu, 2002), as well as hippocampal excitation through the glycine binding site-dependent internalization of NMDARs (Nong et al., 2003; Zhang et al., 2008c). According to these observations, we have proposed that hippocampal glycine and its receptors constitute an effective system in homeostatic regulation of hippocampal synaptic and network plasticity (Zhang et al., 2008a) (Fig. 1).

The role of glycine in regulating hippocampal excitatory neurotransmission has been the subject of several authoritative reviews (MacDonald et al., 2006; Mohler et al., 2008; Wood, 1995), which have mainly addressed the issue of neural plasticity mediated via NMDAR glycine binding site. However, our knowledge of the role of glycine and its receptors in hippocampus is still largely incomplete. Here we review recent evidence of functional implications, neuronal circuitries and mechanisms associated with glycine-mediated signaling in hippocampus, with special emphasis on the inhibitory GlyRs.

2. Glycine in hippocampus

2.1. Glycine transporters in hippocampus

At inhibitory synapses, the postsynaptic actions of glycine are terminated by a rapid reuptake mechanism, which is mainly mediated by glycine transporters (GlyTs). GlyTs, which include GlyT1 and GlyT2, belong to the family of sodium/chloride-dependent transporters (Aragon and Lopez-Corcuera, 2003). GlyT1 is widely expressed in astrocytic glial cells and is thought to control extracellular glycine concentration and regulate excitatory neurotransmission mediated by glycine binding to NMDARs (Bergeron et al., 1998; Johnson and Ascher, 1987). However, recent studies also indicate the neuronal expression of GlyT1 at glutamatergic synapses (Cubelos et al., 2005; Yee et al., 2006). GlyT2 is largely localized to the presynaptic terminals of glycinergic neurons in the brain stem and spinal cord (Zafra et al., 1995), and is thought to provide the principal glycine uptake mechanism at glycinergic synapses. The unique expression patterns of GlyT1 and GlyT2 suggest that they exert distinct functions. Indeed, studies on GlyT1 and GlyT2 knockout mice revealed that they have different effects on glycinergic synaptic transmission (Gomeza et al., 2003a,b). GlyT1 is essential for regulating the level of ambient glycine and thus controlling the functions of both NMDARs and GlyRs. Newborn GlyT1 knockout mice showed severe motor and respiratory deficits and died during the first postnatal day due to increased activation of GlyRs caused by elevated ambient glycine, which resulted in suppressed respiratory activity (Gomeza et al., 2003a). Conditional disruption of GlyT1 in forebrain neurons caused a procognitive and antipsychotic phenotypic profile, indicating a role of GlyT1 in controlling NMDAR functions (Yee et al., 2006). Mice deficient in GlyT2, on the other hand, showed a lethal neuromotor deficiency that resembles severe forms of human hyperekplexia due to the strikingly reduced amplitudes of glycinergic miniature inhibitory postsynaptic currents (IPSCs) (Gomeza et al., 2003b), indicating the crucial function of GlyT2 in efficient transmitter loading of synaptic vesicles in glycinergic nerve terminals (Rousseau et al., 2008; Xu et al., 2005).

In the hippocampus, GlyT1 is mainly expressed in astrocytes and neuronal GlyT1 is only found at glutamatergic synapses (Cubelos et al., 2005), which, when blocked, can facilitate the induction of NMDAR-dependent glutamatergic synaptic plasticity (Martina et al., 2004; Zhang et al., 2008a) (Fig. 1C). On the other hand, the issue whether GlyT2 is expressed in the presynaptic terminals of inhibitory synapses in hippocampus is controversial (Fig. 1A). In general, GlyT2 is not considered to be expressed in hippocampal neurons, consistent with the absence of hippocampal glycinergic synapses (Zafra et al., 1995; Zeilhofer et al., 2005). However, two recent morphological studies have demonstrated the presence of GlyT2 in the hippocampus (Danglot et al., 2004; Song et al., 2006), although this is not supported from the recording of glycinergic synaptic events in hippocampal neurons (Mody et al., 1994; Mori et al., 2002).

Interestingly, GlyTs themselves are highly regulated and subsequently affect the extracellular glycine concentration. GlyTs are downregulated or their uptake function can even be reversed

Download English Version:

https://daneshyari.com/en/article/4353573

Download Persian Version:

https://daneshyari.com/article/4353573

Daneshyari.com