Alexandria Journal of Medicine (2016) **xxx**, xxx–xxx

HOSTED BY

ELSEVIER

Alexandria University Faculty of Medicine

Alexandria Journal of Medicine

http://www.elsevier.com/locate/ajme

Ionotropic glutamate receptors (iGluRs) of the delta family (GluD1 and GluD2) and synaptogenesis

Muhammad Zahid Khan *

Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, China

Received 5 August 2016; accepted 29 September 2016

KEYWORDS

iGluRs;
GluD1;
GluD2;
Synaptogenesis;
Autism spectrum disorder (ASD);
Schizophrenia (SCZ)

Abstract Glutamate delta-1 (GluD1) and glutamate delta-2 (GluD2) form the delta family of ionotropic glutamate receptors (iGluRs) and are distinct from other (iGluRs) in that they do not exhibit typical agonist-induced ion channel currents. Recent studies have demonstrated a crucial role of the delta receptors in synapse formation by interacting with presynaptic proteins such as Neurexin1. This review presents current knowledge regarding the expression, structure and function of Glu delta receptors (GluD1, GluD2) in brain, focusing on synapse formation, function and dysfunction.

Contents

* Address: Department of Pharmacology, China Pharmaceutical University, No. 24 Tong Jia Xiang, Nanjing 210009, Jiang Su Province, China.
E-mail address: mzahidk786@hotmail.com.

Peer review under responsibility of Alexandria University Faculty of Medicine.

http://dx.doi.org/10.1016/j.ajme.2016.09.003

Please cite this article in press as: Khan MZ Ionotropic glutamate receptors (iGluRs) of the delta family (GluD1 and GluD2) and synaptogenesis, *Alex J Med* (2016), http://dx.doi.org/10.1016/j.ajme.2016.09.003

1. Introduction

Glutamate is the main excitatory neurotransmitter in the vertebrate central nervous system. During the quest for ionotropic glutamate receptors (iGluRs) two peculiar candidates, GluRdelta1 (GluD1) and GluRdelta2 (GluD2), were cloned by sequence homology with iGluRs subunits of the AMPA, Kainate, and NMDA subtypes.[5–7] However, delta subunits are unresponsive to glutamate and progress in identifying their functions has been slower than for other iGluRs.[8]

In the central nervous system (CNS), GluD1 is expressed diffusely throughout the forebrain during early development[6,11]; however, its functional significance remains elusive. Recombinant GluD1 is endowed with a functional channel pore domain and promotes synapse formation in vitro.[25–28] GluD1 knockout mice (GluD1 KO) have normal learning in the Morris water maze test and intact hippocampal long-term potentiation.[10] GluD1 is highly expressed in the inner ear hair cells.[9,10] Deletion of GluD1 leads to a deficit in high frequency hearing in mice.[10] Genetic association studies have established the GRID1 gene, which codes for GluD1, as a strong candidate gene for schizophrenia, bipolar disorder, and major depressive disorder.[12–19] GRID1 knockout (KO) mice exhibit behavioral correlates of schizophrenia symptoms, such as hyperaggressiveness and deficits in social interaction.[10,32,48] Copy number variation studies have also implicated GRID1 in autism spectrum disorder (ASD).[20–22] In addition, GRID1 gene is localized to the 10q22–q23 genomic region which is a site for recurrent deletions associated with cognitive and behavioral abnormalities.[23,24]

GluD2 is required for proper development and function of the cerebellum.[1,2] GluD2 acts as a synapse organizer via interactions with postsynaptic scaffold and signaling proteins, and with presynaptic parallel fiber terminals.[1,44,43] Moreover, the metabotropic glutamate receptor mGlu1 associates with GluD2[3] and triggers the opening of the GluD2 channel, which is critically involved in the slow glutamatergic current at the parallel fiber-to-Purkinje cell synapse.[4,3]

2. Expression of GluD1 and GluD2 in mammalian brain

GluD1 is highly expressed in the forebrain including the cortex and hippocampus[6,10,32,37] and recent studies also indicate expression in cerebellar interneurons.[33] In the cortex and hippocampus high level of GluD1 mRNA and protein appears in pyramidal neurons.[10,34,33] Original studies of delta subunits mRNA distribution in the rodent brain report selective GluD2 expression in Purkinje cells and rapid postnatal decrease of GluD1 expression down to low levels in the adult.[5,6] However, subsequent reports indicate that adult expression of both subunits is more widespread than originally described.[10,11,32,36] Recently Hepp et al. used a combination of in situ hybridization, RTPCR, Western blot and immunohistochemistry to characterize the expression patterns of GluD1 and GluD2 in the rodent brain. GluD1 was expressed in neurons throughout the brain, with higher levels in the forebrain and lower levels in the cerebellum. GluD1 was localized at the postsynaptic density of excitatory synapses on hippocampal pyramidal cells. GluD2 expression was also widespread but was markedly enriched in the cerebellum. Likewise, the GluD1/GluD2 mRNA ratio was high in the cortex and low in the cerebellum.[29] Their results support a role for the delta family of glutamate receptors in neuronal networks throughout the adult brain.

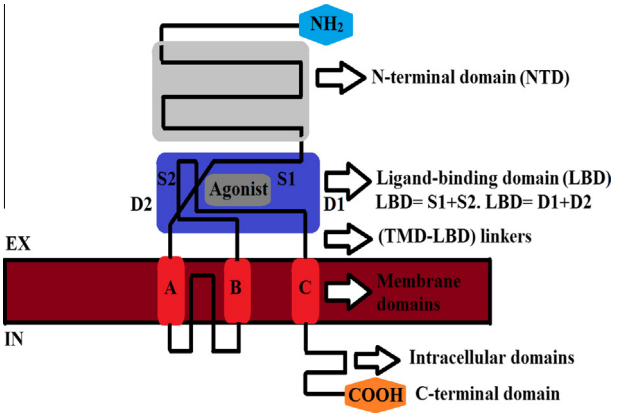

Figure 1 Modular domain structure of delta receptors (GluD1, GluD2). Four subunits assemble to form a functional receptor. NTD, N-terminal domain; S1 and S2, sequence segments that form the ligand binding domain (LBD); D1 and D2, globular domains of the LBD, corresponding to the two lobes of the clamshell-like structure; A, B, C, transmembrane domains.

3. Molecular structure of GluD1 and GluD2

GluD1 and GluD2 consist of a N-terminal domain and a bipartite ligand-binding domain on the extracellular side of the plasma membrane, three transmembrane domains and an ion-channel-forming re-entrant loop segment, and a cytoplasmic C-terminal domain. Four subunits assemble to form a functional receptor. NTD, N-terminal domain; S1 and S2, sequence segments that form the ligand binding domain (LBD); D1 and D2, globular domains of the LBD, corresponding to the two lobes of the clamshell-like structure; A, B, C, transmembrane domains; P, pore helix and pore loop; CTD, C-terminal domain. The main difference between delta receptors and other ionotropic glutamate receptors lies within their LBDs. However, there are also some subtle differences in electrophysiological and gating properties, demonstrating that in delta receptors the ion channel and the linkers are connecting it to the LBD function slightly differently than in other glutamate receptors[26] Fig. 1.

4. Role of GluD1 receptor in synaptogenesis

Synaptogenesis is the formation of synapses between neurons in the nervous system. Although it occurs throughout a healthy person's life span, an explosion of synapse formation occurs during early brain development, known as exuberant synaptogenesis.[39] During development, early spherical neural progenitor cells give rise to many processes, the neurites; one of these early neurites subsequently transforms into an axon while others develop into dendrites. The growing axons that come in contact with other neurons form terminal presynaptic swellings. These presynaptic swellings possess specific neurotransmitter as well as cognate receptors; they also influence the post-synaptic neurons to express desired receptors. The

Please cite this article in press as: Khan MZ Ionotropic glutamate receptors (iGluRs) of the delta family (GluD1 and GluD2) and synaptogenesis, *Alex J Med* (2016), http://dx.doi.org/10.1016/j.ajme.2016.09.003