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

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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

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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.

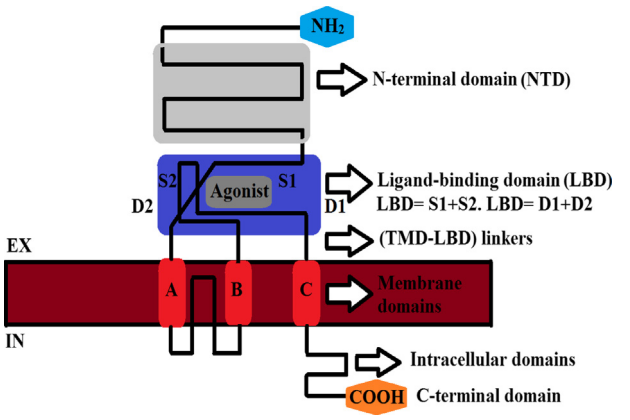

Figure 1 Modular domain structure of delta receptors (GluD1, GluD2). Four subunits assemble to form a functional receptor. NTD, N-terminal domain; S1 and S2, sequence segments that form the ligand binding domain (LBD); D1 and D2, globular domains of the LBD, corresponding to the two lobes of the clamshell-like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

number of presynaptic swellings, their morphometric characteristics, receptor decoration and other properties may be increased, modified or lost. These individual or collective changes influence somatic and autonomic behaviors including cognition as well as consciousness, sensitivity, new and/or existing learning and memory, or recovery processes following an injury or a disease.[40–42]

Recent studies have demonstrated a crucial role of the delta receptors in synapse formation by interacting with presynaptic proteins such as Neurexin1.[43,44,27,46] Although the synaptic function of GluD2 expressed in Purkinje cells has been extensively studied, the function of GluD1 in native system remains poorly understood. Yadav et al. showed that deletion of GluD1 leads to abnormal emotional and social behaviors. They found that GluD1 knockout mice (GluD1 KO) were hyperactive, manifested lower anxiety-like behavior, depression-like behavior in a forced swim test and robust aggression in the resident-intruder test. Chronic lithium rescued the depression-like behavior in GluD1 KO. GluD1 KO mice also manifested deficits in social interaction. They proposed that deletion of GluD1 leads to aberrant circuitry in prefrontal cortex and amygdala owing to its potential role in presynaptic differentiation and synapse formation.[32] In another study Yadav et al., evaluated GluD1 KO in learning and memory tests. They proposed that GluD1 receptor is essential for normal synapse formation and maintenance and deletion of GluD1 leads to synaptic abnormalities in the amygdala, prefrontal cortex and hippocampus that lead to social and emotional deficits as well as deficits in learning and memory.[48] The results of Gupta et al., demonstrated a critical role of GluD1 in maintaining spine dynamics. They found that pyramidal neurons in adult GluD1 KO medial prefrontal cortex (mPFC) and hippocampus have higher dendritic spine number that may occur due to impaired spine pruning or excessive spine generation. They also observed abnormalities in LIMK1-cofilin signaling which is involved in regulating spine dynamics and a lower NMDA receptor GluN2A/GluN2B subunit expression ratio suggesting a potential impairment in the GluN2B to GluN2A developmental switch. Moreover, inhibition of GluN2B-containing receptors was found to reverse signaling abnormalities and spine density as well as stereotyped behavior and depression-like behavior in GluD1 KO mice[37] Fig. 2. These results may have implications for disorders such as autism spectrum disorder (ASD).

5. Role of GluD2 receptor in cerebellar long-term depression (LTD) and synaptogenesis

GluD2 receptors are predominantly localized in the postsynaptic density of excitatory synapses in the central nervous system (CNS). GluD2 was previously designated as an "orphan" iGluR, as no endogenous ligands had been identified that could bind and activate the receptor.[5,6] D-Ser and glycine have now been identified as ligands for GluD2.[51]

The role of GluD2 in the CNS is most studied in the cerebellum, where GluD2 receptors are expressed in glutamatergic synapses of the Purkinje-type neurons.[52–54] A key role for GluD2 in postsynaptic functions in cerebellar Purkinje neurons, including induction of cerebellar long-term depression (LTD), a form of synaptic plasticity that underlies motor learning, has been demonstrated.[52,75] Endogenous D-Ser binding to GluD2 has been shown to regulate LTD in Purkinje neurons.[55] This modulation required the intact intracellular C-terminal domain (CTD) of GluD2, which interacts with a range of scaffolding and signaling proteins.[73] C-terminal portion of GluD2 consists of a PDZ binding motif, to which PDZ proteins, such as PSD-93, protein tyrosine phosphatase (PTPMEG), synaptic scaffolding molecule SSCAM, n-PIST, and delphilin can bind.[54] Furthermore, D-serine released from Bergmann glia can bind to the ligand binding domain of GluD2 and induce AMPA receptor endocytosis and LTD.[55] Similarly, application of an antibody against the

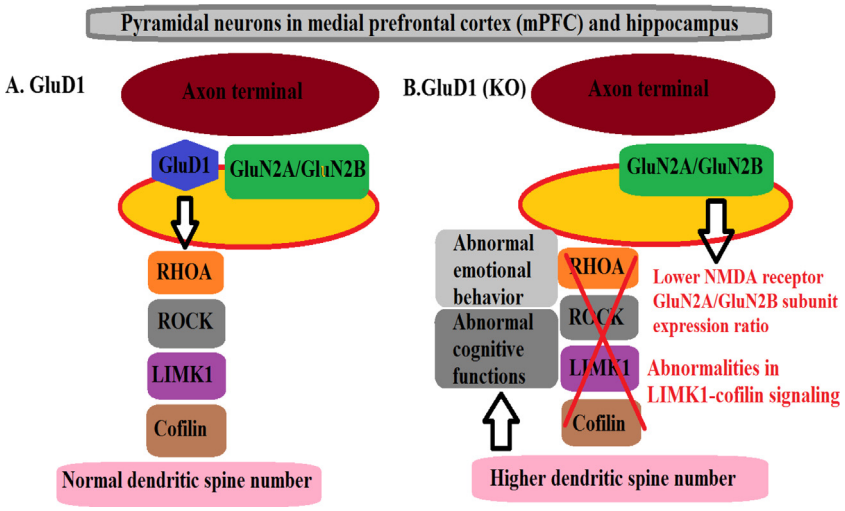

Figure 2 Signaling pathway of GluD1 receptor in the pyramidal neurons in medial prefrontal cortex (mPFC) and hippocampus. A normal LIMK1-cofilin signaling and expression of NMDA receptor GluN2A/GluN2B subunit expression ratio and normal dendritic spine number in the pyramidal neurons in the presence of GluD1 receptor in medial prefrontal cortex (mPFC) and hippocampus. B show abnormalities in LIMK1-cofilin signaling and lower expression of NMDA receptor GluN2A/GluN2B subunit expression ratio, higher dendritic spine number in the GluD1 KO in the pyramidal neurons in medial prefrontal cortex (mPFC) and hippocampus and abnormal emotional behavior and abnormal cognitive functions in mice.

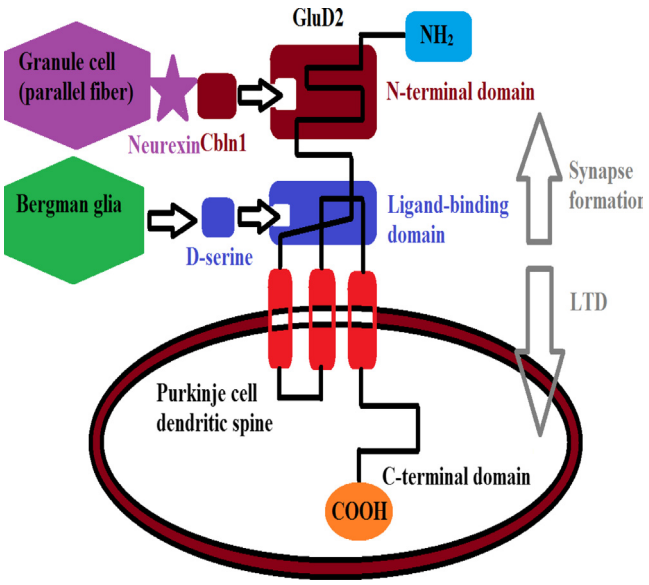

Figure 3 GluD2 signaling pathway. Cbln1 released from parallel fibers (the axons of the granule cells) binds to neurexin containing splice-site 4 (S4+) at the presynaptic site and the N-terminus of GluD2 at the postsynaptic site. The neurexin/Cbln1/GluD2 tripartite complex traverses the synaptic cleft and may function as a bidirectional synaptic organizer. D-serine released from Bergmann glia binds to the ligand-binding domain of GluD2 and regulates AMPA receptor endocytosis and long-term depression (LTD) via the C-terminus of GluD2.

ligand-binding domain of GluD2 induces AMPA receptor endocytosis and LTD in the wild-type adult cerebellum.[52] Importantly, D-serine binding to GluD2 fails to induce LTD when the C-terminal domain is deleted or when PKC inhibitory peptide is included in the patch pipette.[55] It can be speculated that D-Ser binding to the extracellular LBD may induce conformational changes at the CTD that potentially control GluD2 interactions with intracellular effector proteins required for LTD induction.

In addition to a direct signaling role, the extracellular part of GluD2 binds the protein Cbln1, which is secreted from cerebellar granule cells, and this interaction is essential for synapse integrity between Purkinje cells and cerebellar granule cells in adult mice.[58,44,60–62,75] Together, these results indicate that GluD2 contributes to two major functions at PF–Purkinje cell synapses—synapse formation/maintenance and LTD induction.

Precise neuronal circuitry is established by the coordinated formation of excitatory and inhibitory synapses. A loss of balance between excitation and inhibition leads to aberrant information processing, which is associated with various forms of neurodevelopmental and neuropsychiatric disorder.[63–67] Purkinje cells (PCs), which send the only output from the cerebellar cortex, receive two excitatory inputs, from parallel fibers (PFs; axons of the granule cells) and climbing fibers; they receive inhibitory input from two groups of molecular-layer interneurons (MLIs), basket cells and stellate cells. A key molecule that induces excitatory synaptogenesis between PCs and PFs is Cbln1, a C1q-family glycoprotein that is secreted from PFs. Among synapse organizers, Cbln1 is unique because it is indispensable for the formation and maintenance of synapses in vivo.[68,69,61] The role of Cbln1 in excitatory synaptogenesis is well defined, whether and how Cbln1 regulates inhibitory synapses on PCs has remained unclear. A recent study by Ito-Ishida et al., showed that Cbln1–GluD2 signaling shifts the excitatory–inhibitory balance toward excitation in PCs, by downregulating MLI–PC synapses while increasing the number of excitatory synapses from PFs[72] Fig. 3. Because activation of MLI–PC synapses is essential to fine-tune the onset of PC action potentials, which regulate motor coordination and learning,[70,71] it can be speculated that the Cbln1-mediated suppression of MLI–PC synapse functions has a significant physiological impact on such behaviors.

6. Concluding remarks

Defects in synapses, including their formation, function, and maintenance, however, are of particular interest not only because they are basic functional units of the brain and continue to be modified by experience throughout life, but also because molecular and structural changes occurring in synapses may be the most immediately targetable for therapeutic interventions after birth.[76–79] Recent studies have demonstrated a crucial role of the delta receptors (GluD1, GluD2) in synapse formation.

A major hypothesis for the underlying etiology of autism and SCZ is that of synaptic dysfunction. Recent studies have implicated GRID1 in autism spectrum disorder (ASD) and SCZ. GRID1 knockout (KO) mice exhibit behavioral correlates of schizophrenia symptoms, such as hyperaggressiveness and deficits in social interaction.[10,32,48] Studies have shown that delta receptors (GluD1, GluD2) play significant role in synapse formation and might play a role in the underlying pathophysiology of the autism and SCZ. However, there is a lack of clear data supporting its role in autism and SCZ; therefore, complementary studies are needed to fully clarify delta receptors functions. This emphasizes the need to evaluate its role in the brain by using different animal models of the autism and SCZ.

Conflict of interest

The author declare that there is no conflict of interest.

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