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Inside story of Group I Metabotropic Glutamate Receptors (mGluRs)

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ABSTRACT

Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors (GPCRs) that are activated by the neurotransmitter glutamate in the central nervous system. Among the eight subtypes, mGluR1 and mGluR5 belong to the group I family. These receptors play important roles in the brain and are believed to be involved in multiple forms of experience dependent synaptic plasticity including learning and memory. In addition, group I mGluRs also have been implicated in various neuropsychiatric disorders like Fragile X syndrome, autism etc. The normal signaling depends on the precise location of these receptors in specific region of the neuron and the process of receptor trafficking plays a crucial role in controlling this localization. Intracellular trafficking could also regulate the desensitization, resensitization, down-regulation and intracellular signaling of these receptors. In this review I focus on the current understanding of group I mGluR regulation in the central nervous system and also their role in neuropsychiatric disorders.

1. Introduction

The major excitatory neurotransmitter Glutamate activates two types of receptors, viz., ionotropic glutamate receptors and metabotropic glutamate receptors in the central nervous system (CNS) (Pin and Duvoisin, 1995; Dhami and Ferguson, 2006). Ionotropic receptors are ion channels that allow cations to go through them and there are three types of ionotropic glutamate receptors present in the central nervous system viz., *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (Nakanishi, 1994; Huganir and Nicoll, 2013). The naming has been done based on their agonist preference. The metabotropic glutamate receptors (mGluRs) are members of class C G-protein coupled receptor (GPCR) family and they have been subdivided into three classes based on the sequence similarity, the second messenger pathways that they initiate upon activation and pharmacology (Nakanishi, 1994; Pin and Duvoisin, 1995; Conn and Pin, 1997). mGluR1 and mGluR5 belong to the group I family, group II consists of mGluR2 and mGluR3 and group III has mGluR4, mGluR6, mGluR7 and mGluR8 as members. Among these three groups group I mGluRs are primarily localized at the post-synaptic sites, group II mGluRs are expressed at both pre and post-synaptic sites and group III mGluRs are predominantly expressed at the pre-synaptic neurons where they have been reported to regulate the release of neurotransmitters (Baude et al., 1993; Shigemoto et al., 1993). These members of the mGluR family activate various second messenger pathways on ligand binding. Group I mGluRs are predominantly positively coupled to Gαq-linked pathway, which generates diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) (Conn and Pin, 1997; Kim et al., 2008). Group II and group III mGluRs are linked with Gαi/o which leads to the inhibition of adenylate cyclase and thereby inhibition of cAMP formation (Schoepp, 2001; Pin and Acher, 2002). mGluRs are also present in glial cells in the central nervous system where they play crucial roles in glial-neuron communication, in neuroprotection and in glutamate release (Winder and Conn, 1996; Yao et al., 2005). mGluRs have been demonstrated to play crucial roles in various forms of synaptic plasticity, including learning and memory as well as in neuronal development (Lee, 2006; Citri and Malenka, 2008; Ronesi and Huber, 2008a; Gladding et al., 2009; Tsanov and Manahan-Vaughan, 2009). They have also been implicated in various neuropsychiatric disorders like Fragile X syndrome, schizophrenia, autism etc. (Dolen et al., 2007; Ronesi and Huber, 2008b; Niswender and Conn, 2010). This review focuses on the above aspects of group I mGluRs in detail.

2. Group I mGluRs distribution and signaling

Group I mGluRs are differentially distributed in various regions of the central nervous system. mGluR1 has been observed to be highly expressed in CA3 region of the hippocampus, cerebellum,

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olfactory bulb, and thalamus. The other member of same family, mGluR5 is expressed in the CA1 and CA3 region of the hippocampus, cortex, striatum and olfactory bulb. It is also expressed in the cerebellum, but at a low level (Bordi and Ugolini, 1999). These receptors show subtype-specific regulation in their localization and expression during development of the brain which suggests a very dynamic and differential pattern of expression during the brain development (Catania et al., 1994; Lopez-Bendito et al., 2002). For example, mGluR1 expression showed a steady increase in both hippocampus and neocortex during development (Shigemoto et al., 1992; Catania et al., 1994). Similarly, in cortex the expression of mGluR5a increases and reaches a peak during second postnatal week and subsequently comes down (Catania et al., 1994; Romano et al., 1996). On the other hand, the expression of mGluR5b mRNA levels increases postnatally and in adult it is the predominant form of mGluR5 (Minakami et al., 1995; Romano et al., 1996). It has become very clear that although mGluR1 and mGluR5 belongs to the same group their expression is differentially regulated. This differential expression of the two subtypes of group I mGluRs correlate very well with differential regulation of CA1 pyramidal cell function in the hippocampus as observed by electrophysiological studies (Mannaioni et al., 2001). Work done by multiple groups have suggested that group I mGluR activation and expression pattern might regulate various aspects of neurogenesis and synaptogenesis during development of the cortex (Romano et al., 1996; Furuta and Martin, 1999; Munoz et al., 1999; Martinez-Galan et al., 2001). The above and many other studies suggest that the pattern of distribution of group I mGluRs in a region of the brain correlates very well with their distinct functions. Immunocytochemical and electron microscopy studies have suggested that mGluR1 and mGluR5 are perisynaptically localized and they are primarily localized in the post-synaptic neurons (Lujan et al., 1996). Other than the central nervous system group I mGluRs are also present in outside the brain as well where they play various important roles. For example, they are present in the skin cells where mGluRs play crucial role in pain sensation (Bhave et al., 2001). They are also expressed in osteoblasts, hepatocytes, and heart cells.

Both mGluR1 and mGluR5 share a large extracellular domain where the natural ligand binds and a seven transmembrane domain (7TM) which contains the binding site for the synthetic allosteric modulators. The crystal structure of the ligand binding domain of mGluR1 suggests that it is comprised of two globular domains separated by a hinge region (Kunishima et al., 2000). In the absence of the ligand the receptor exist in open (resting) and closed (active) form. Binding of the ligand stabilizes the closed (active) form (Kunishima et al., 2000; Tsuchiya et al., 2002). The crystal structures of the isolated 7TM domain of both human mGluR1 and mGluR5 have been solved (Dore et al., 2014; Wu et al., 2014). One of the interesting observations from these structural studies was that the 2nd extracellular loop of mGluR1 adopts a large β-hairpin conformation similar to that observed in the class A GPCRs. Furthermore, the transmembrane region of mGluR1 is capable of forming dimers through TM1–TM1 interactions and interestingly these interactions are stabilized by the cholesterol molecules (Wu et al., 2014). Activation of mGluR1 and mGluR5 has been reported to induce different oscillatory responses of distinct frequencies largely due to a single amino acid residue in the G-protein coupling domain of mGluR1 (D854) and mGluR5 (T840) (Kawabata et al., 1996; Dale et al., 2001a). The lipid environment of the plasma membrane could also influence the activity of group I mGluRs. Both mGluR1 and mGluR5 were seen to be present with membranes enriched in lipid raft-associated proteins and lipids (Burgueno et al., 2003; Francesconi et al., 2009). However, only a fraction of these receptors were observed to be associated with lipid rafts rich membrane suggesting that either group I mGluRs have low affinity for rafts or the association is transient. Interestingly, the association of lipid rafts with mGluR1 has been reported to increase by agonist binding and this phenomenon depends on the membrane cholesterol content (Kumari et al., 2013). The TM5 and the third intracellular loop of the receptor contains a cholesterol binding motif and increase in the cholesterol levels in the membrane enhances the agonist-mediated activation of the receptor, whereas, depletion of the cholesterol inhibits the mGluR1-dependent ERK activation (Kumari et al., 2013). All these data suggest that lipid rafts and membrane cholesterol positively influence the group I mGluR signaling.

As stated before, group I mGluRs are positively coupled to the IP_3-Diacylglycerol (DAG) pathway. Thus, upon binding with the ligand these receptors positively couple to phospholipase C (PLC) via $G_{\alpha q/11}$ (Abdul-Ghani et al., 1996). Subsequently, intracellular rise in Ca^{2+} concentration leads to the activation of protein kinase C (PKC). Group I mGluRs activates PKC in a most canonical way. Activation of conventional PKC isotypes depends on the intracellular rise in Ca^{2+} and most isotypes of PKC requires DAG in addition to Ca^{2+} for their activity. Group I mGluRs activation leads to the hydrolysis of PIP_2, which in turn forms IP_3 and DAG, thus satisfying both requirements for activation of PKC. Subsequently, IP_3 induces the release of Ca^{2+} from the intracellular stores. Although, the primary coupling of the group I mGluRs are with $G_{\alpha q/11}$, overexpression of these receptors in HEK293 and CHO cells leads to the coupling of these receptors with $G_{\alpha s}$ and $G_{\alpha i/o}$ as well (Aramori and Nakanishi, 1992; Francesconi and Duvoisin, 2000). For example, overexpression of mGluR1a in CHO cells leads to the stimulation of cAMP pathway (Aramori and Nakanishi, 1992). Among the two subtypes of group I mGluRs, mGluR1 shows less discrimination in terms of its coupling to $G_{\alpha s}$ and $G_{\alpha i/o}$. The above examples suggest that in the above mentioned heterologous systems group I mGluRs could couple to a variety of G-proteins. It is due to this reason, understanding the precise coupling of the endogenous receptors in its native environment, i.e., in various types of neurons is crucial to study, which will enable us to understand the signaling mechanisms of these receptors *in vivo*. In various systems, such as, hippocampal cells and cultured cortical glial cells activation of group I mGluRs ultimately activates the MAP kinase pathway (Peavy and Conn, 1998; Gallagher et al., 2004). This mGluR-mediated MAP kinase activation has been reported to be involved in the mGluR-dependent long term depression (LTD) in pyramidal hippocampal neurons. The scaffolding protein Homer1b/c, which interacts with group I mGluRs, has been postulated to be involved in this process (Mao et al., 2005). Group I mGluRs also regulate certain functions of the brain through tyrosine kinases. Nonreceptor tyrosine kinase like src plays important role in various mGluR dependent processes like, mGluR-mediated increase in the NMDAR current, phosphorylation of NMDARs etc. (Heidinger et al., 2002; Guo et al., 2004).

3. Role of group I mGluRs in synaptic plasticity and neuropsychiatric disorders

The adult brain shows remarkable plasticity which enables us to learn new skills and establish new memories. Principle neurons in the central nervous system contains on average 10,000 synapses. The activity-dependent changes in the efficacy and strength of the synaptic transmission at pre-existing synapses is referred as synaptic plasticity. Works done in last 4 decades have suggested that synaptic plasticity is not only involved in the learning and memory formation, it is also believed to play critical roles in the circuit formation in the developing brain (Citri and Malenka, 2008). Evidence is also accumulating that impairment of synaptic plasticity could be a leading reason for many neuropsychiatric disorders. It was widely believed that the reason a new experience modifies our subsequent behaviour is controlled, at least partially, through