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Invited review

Role of metabotropic glutamate receptors in persistent forms of hippocampal plasticity and learning

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ABSTRACT

Storage and processing of information at the synaptic level is enabled by the ability of synapses to persistently alter their efficacy. This phenomenon, known as synaptic plasticity, is believed to underlie multiple forms of long-term memory in the mammalian brain. It has become apparent that the metabotropic glutamate (mGlu) receptor is critically required for both persistent forms of memory and persistent synaptic plasticity. Persistent forms of synaptic plasticity comprise long-term potentiation (LTP) and long-term depression (LTD) that last at least for 4 h but can be followed in vivo for days and weeks. These types of plasticity are believed to be analogous to forms of memory that persist for similar time-spans. The mGlu receptors are delineated into three distinct groups based on their G-protein coupling and agonist affinity and also exercise distinct roles in the way they regulate both long-term plasticity and long-term hippocampus-dependent memory. Here, the mGlu receptors will be reviewed both in general, and in the particular context of their role in persistent (>4 h) forms of hippocampus-dependent synaptic plasticity and memory, as well as forms of synaptic plasticity that have been shown to be directly regulated by memory events.

This article is part of a Special Issue entitled 'Metabotropic Glutamate Receptors'.

1. Introduction

Glutamate is one of the most important excitatory neurotransmitters in the central nervous system (CNS) and plays an important role in various integrative brain functions, as well as in brain development. Glutamate generally mediates fast excitatory transmission across the nervous system. This effect is enabled by fast-acting ligand-gated ionotropic glutamate (iGlu) receptor channels, namely the N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and Kainate iGlu receptors. Glutamate also acts through more slowly activating G-protein-bound receptors, which act via 2nd messenger systems. These glutamatergic receptors modulate cellular excitability and synaptic transmission and are referred to as metabotropic glutamate (mGlu) receptors. They exhibit a widespread distribution in the CNS and play a major role in various neuronal processes including synaptic plasticity and memory formation.

1.1. Subtypes of mGlu receptors

The very first description of mGlu receptors occurred when two different labs cloned and isolated the first mGlu receptor encoding cDNA (Houamed et al., 1991; Masu et al., 1991) termed mGlu1a. Analysis of the amino acid sequence of the first mGlu receptor revealed a quite distinct identity of the receptor from iGlu receptors, owing to their large extracellular N-terminal domain, a seven transmembrane domain and a large C-terminal domain. By screening several cDNA libraries using mGlu1a sequence as a probe, scientists isolated eight other genes and several splice variants that encode mGlu receptors to date (Tanabe et al., 1992; Pin et al., 1992; Abe et al., 1992; Nakajima et al., 1992; Okamoto et al., 1994; Saugstad et al., 1994; Joly et al., 1995, 1995; Minakami et al., 1994; Minakami et al., 1994; Duvoisin et al., 1995; Iversen et al., 1994; Laurie et al., 1996, 1997). Amino acid sequencing of mGlu receptors reveal no sequence homology with other G-protein coupled receptors, suggesting that the mGlu receptors comprise a new receptor gene family. Along with Ca^{2+}-sensing receptors, putative pheromone receptors and $GABA_B$ receptors (Bockaert and Pin, 1999), mGlu receptors are a member of the family 3 of G -protein -coupled receptors (GPCRs).

Mainly based on their sequence similarity, but also on their transduction mechanisms and pharmacological properties, mGlu

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receptors have been classified into 3 groups (Pin and Duvoisin, 1995; Nakanishi, 1994) (Table 1). Intra-group sequence similarity is about 60–70%, whereas by comparing between groups the similarity falls to 40–45%. Group I mGlu receptors comprise mGlu1 and mGlu5, which activate Gq proteins, whereas group II and group III mGlu receptors are coupled to pertussis toxin sensitive G-proteins, and comprise mGlu2, 3 (group II) and mGlu 4, 6, 7 and 8 (group III).

1.2. Splice variations

With the exception of mGlu2, splice variants have been identified for all mGlu receptors (Table 1). Six distinct types of C-terminal splice variants have been reported for the mGlu1 gene (Hermans and Challiss, 2001), namely mGlu1a, 1b, 1c, 1d, 1e and 1f of which the longest is mGlu1a (Pin and Duvoisin, 1995; Soloviev et al., 1999; Hermans and Challiss, 2001). MGlu5 exists as two main isoforms, mGlu5a and mGlu5b (Joly et al., 1995). Other isoforms such as mGlu5c, 5d and 5e have been reported in humans (Minakami et al., 1994).

Exon-skipping events lead to three spliced variants in mGlu3 (Sartorius et al., 2006). For group III receptors, mGlu4 exists as mGlu4a, and mGlu4b (Thomsen et al., 1997). Three mGlu6 isoforms have been reported. One mGlu6b in rat retina forms a 508 amino acid truncated protein due to insertion of an in frame stop codon. Human retina has two isoforms, hmGlu6b and hmGlu6c, consisting of 425 and 405 amino acids. Both rat and human protein lack the TM and intracellular portions, thus are secreted and might act as soluble glutamate receptors or as a dominant negative receptor variant (Valerio et al., 2001). MGlu7 and 8 isoforms have been identified from rat brain (Corti et al., 1998). MGlu7 forms five C terminal-end isoforms: mGlu7a to mGlu7e (Niswender and Conn, 2010). MGlu8 reported forms three isoforms, mGlu8a–c and 8b (Pin and Duvoisin, 1995; Malherbe et al., 1999). The splicing site in mGlu7 is analogous to mGlu1, 4 and 5 (Corti et al., 1998); showing conservation of this site in many mGlu receptor genes (Conn and Pin, 1997).

1.3. Pharmacological properties

The pharmacology of the mGlu receptors is mainly based on two types of distinctly acting ligands. The classical competitive ligands exert clear agonist and antagonist effects, acting via the orthosteric ligand binding site in the N-terminal domain (Table 1). The other type consists of the emerging class of non-competitive ligands, comprising various allosteric modulators that bind the transmembrane domain of mGlus (Table 1). Many of the competitive ligands, which mostly comprise constrained or substituted amino acid analogues, have greatly enabled the study of various effects of mGlus. But their utility is limited due to their limited CNS bioavailability and poor pharmacokinetic properties. Also the evolutionary-conserved structure of the ligand-binding domain has hindered the identification of individually-selective competitive mGlu ligands. This has been overcome by usage of the non-competitive ligands, that have better selectivity and bioavailability. A very detailed overview of the pharmacological properties of metabotropic glutamate receptors is beyond the scope of this review, and has been extensively reviewed elsewhere (Niswender and Conn, 2010; Pin and Acher, 2002; Conn and Pin, 1997; Kew and Kemp, 2005).

Table 1
Table provides an overview of the cellular localization, hippocampal distribution, signaling pathways and G-protein coupling of the mGlu receptors.

Group	Subtype	Cellular localisation	Hippocampal distribution	Signalling pathways and G-protein coupling
I	mGlu1	Mainly postsynaptic, also present on interneurones[a]	Cell layers of the CA1 and the dendritic fields of the CA3 and DG. (mGlu1a on interneurones, mGlu1b on CA3 pyramidal neurones, & on DG granule cells)[b]	Gq-coupled:[c] Stimulates PLC. Increases DAG and IP_3 and intracellular Ca^{2+}
	mGlu5	Mainly postsynaptic, also present on interneurones[d,e,f,g]	dendritic fields of CA1 neurons, as well as DG (strong expression) and CA3[h]	
II	mGlu2	Mainly presynaptic[i]	pre-synaptic boutons of the mossy fibres and the perforant path[i]	Gi/Go-coupled:Inhibits adenylyl cyclase; decreases cAMP and intracellular Ca^{2+}; act as autoreceptors for glutamate
	mGlu3	Neurones (mainly presynaptically) and astrocytes[j,k]	Molecular layer of dentate gyrus, entorhinal and subicular cortex[l]	
III	mGlu4	Mainly presynaptic[k]	CA1-CA3 regions (albeit low expression)[i]	Gi/Go-coupled: Inhibit adenylyl cyclase[m]; decrease cAMP and cGMP and intracellular Ca^{2+}; act as auto–receptors for glutamate[q].
	mGlu6	Postsynaptic[n]	Only found in retina[n]	
	mGlu7	Presynaptic[o]	CA1 and DG; active zones of presynaptic terminals[o]	
	mGlu8	Presynaptic[p]	Colocalises with mGlu7, also found on perforant path terminals[p]	

Abbreviations: cyclic adenosine monophosphate (cAMP); cyclic guanosine monophosphate (cGMP); dentate gyrus (DG); diacyl glycerol (DAG); inositol trisphosphate (IP_3) phospholipase C (PLC).

[a] Ferraguti et al., 1998.
[b] Mateos et al.,1998.
[c] Pin and Duvoisin 1995.
[d] Shigemoto et al., 1995.
[e] Takumi et al., 1999.
[f] Kerner et al., 1997.
[g] Baude et al., 1993.
[h] Lujan et al., 1996, 1997.: Hanson and Smith, 1999.
[i] Ferraguti and Shigemoto, 2006.
[j] Ohishi et al., 1993.
[k] Tanabe et al.,1993.
[l] Tamaru et al., 2001.
[m] Conn and Pin, 1997.
[n] Nomura et al., 1994.
[o] Okamoto et al., 1994.
[p] Corti et al., 1998.
[q] Macek et al ., 1996.