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Review

Group 5 metabotropic glutamate receptors: Role in modulating cortical activity and relevance to cognition

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ABSTRACT

Group 5 metabotropic glutamate ($mGlu_5$) receptors are abundant in forebrain and limbic regions and provide a novel pharmacological target for modulation of cognition. Here, we review recent advances in understanding the electrophysiology of these receptors which reveal a role for $mGlu_5$ receptors in the regulation of tonic and bursting modes of neuronal firing, maintenance of distinct forms of synaptic plasticity, and reversal of detrimental effects of NMDA receptor antagonism on cortical neuronal activity. Furthermore, recordings using recently developed positive allosteric modulators of the $mGlu_5$ receptor suggest that these agents have an electrophysiological profile comparable to the antipsychotic agent clozapine. These findings, in conjunction with behavioral evidence from preclinical studies of cognition, suggest a potential precognitive profile for the $mGlu_5$ receptor potentiators.

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1. Introduction

Excitatory transmission through glutamate receptors constitutes the main mode of synaptic signaling in the brain regions that are critical for cognition. Among various subtypes of glutamate receptors, the role of ionotropic NMDA or AMPA receptors in the maintenance of cognitive functions including learning, memory, attention, and behavioral flexibility has long been established. Furthermore, malfunction of neurotransmission mediated by these receptors, particularly the NMDA receptor, is believed to play a key role in several cognitive disorders such as schizophrenia (Coyle, 1996; Moghaddam, 2003; Tamminga, 1998). Accordingly, improvising tools to control the flow of excitatory neurotransmission has been a major goal of drug development in the past two decades. The widespread distribution of ionotropic receptors, including their participation in vital homeostatic functions, has, however, confounded the attempts to directly target these receptors. The more recently discovered metabotropic glutamate receptors (mGluRs) may provide a more feasible option to regulate excitatory neurotransmission without the more serious side effects that may be associated with ionotropic drugs. The mGluRs are particularly promising as pharmacological targets because these receptors have a more limited distribution than ionotropic drugs, with the highest concentration of several subtypes in forebrain areas, and act as slow-paced modulators of fast ionotropic receptors. Together, these properties suggest that mGluRs have the potential to fine-tune the chemical basis of cognition without interfering with the brain's vital functions. Recent development of conformationally modulated analogues of glutamate have allowed selective targeting of specific subtypes of mGluRs, opening the path for a better

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characterization of the role of each subtype in regulation of neuronal activity. Here we will focus on metabotropic glutamate 5 ($mGlu_5$) receptor that, based on its functional properties and recent findings, may be of special interest for modulating glutamatergic control of cognition.

2. The basic neurophysiological characteristics of $mGlu_5$ receptor

Group I mGluRs, including mGlu1 and $mGlu_5$ receptors, have a predominantly postsynaptic distribution and act primarily through activation of Gq-protein signaling and activation of phospholipase C (Baude et al., 1993; Lujan et al., 1996; Tanaka et al., 2000). Among these subtypes, the $mGlu_5$ receptors are mostly present in corticolimbic areas that control the higher cognitive and incentive functions in the brain including the medial prefrontal and orbitrofrontal cortices, hippocampus, cingulate, striatum and septal nuclei (Bell et al., 2002; Romano et al., 1995; Shigemoto et al., 1993). This combination of location and slow mode G-protein transmission may serve as a basis for selective involvement of the $mGlu_5$ receptor in regulation of cognitive tasks (Ayala et al., 2009; Balschun et al., 1999; Homayoun et al., 2004; Kinney et al., 2003; Lu et al., 1997; Semenova and Markou, 2007; Xu et al., 2009). For example, the $mGlu_5$ receptor antagonists dose-dependently impair working memory, and instrumental and spatial learning (Balschun and Wetzel, 2002; Homayoun et al., 2004; Manahan-Vaughan and Schuetz, 2002; Naie and Manahan-Vaughan, 2004), suggesting that tonic activation of the $mGlu_5$ receptor is required for the maintenance of these cognitive tasks. More recently, strategies aimed at potentiating the $mGlu_5$ receptor by targeting an allosteric modulatory site on this receptor improve cognitive performance in paradigms such as novel object recognition, five-choice serial reaction time test, and Morris water maze (Ayala et al., 2009; Balschun et al., 2006; Liu et al., 2008). Thus, the potential procognitive efficacy of $mGlu_5$ receptor positive modulators and mechanisms that mediate this action are of intense interest.

Several electrophysiological studies have provided clues on how $mGlu_5$ receptors may modulate cognitive functions. First, the activation of the $mGlu_5$ receptor produces direct excitatory effects, e.g. excitatory postsynaptic potentials (EPSPs), in *in vitro* preparations of the subthalamic nucleus (Awad et al., 2000), hippocampus (Fitzjohn et al., 1999), substantia nigra pars reticulata (Marino et al., 2001), and septohippocampal cholinergic neurons (Wu et al., 2004). For example, in the subthalamic nucleus, the activation of $mGlu_5$ receptor induces a direct excitation that is characterized by depolarization, increased firing frequency, and increased burst-firing activity (Awad et al., 2000). These excitatory properties of the $mGlu_5$ receptor have been linked to a reduction of calcium-dependent potassium conductance and accumulation of intracellular Ca^{++} concentration in hippocampus (Mannaioni et al., 2001). Another form of direct excitatory influence of the $mGlu_5$ receptor has been described in hippocampal slices treated with GABA antagonists, bicuculline and picrotoxin, where $mGlu_5$ receptor activity contributes to persistent bursts of spiking (Lee et al., 2002; Merlin, 2002; Stoop et al., 2003). The latter findings suggest that the $mGlu_5$ receptor may tonically participate in the prolongation of excitatory activity. This property is likely to contribute to the maintenance of cognitive functions in physiological conditions, where bursting is considered an efficient mode of information transmission between individual cells as well as at the network level. It has also been suggested that a breakdown in the regulatory mechanisms controlling the $mGlu_5$ receptor-mediated firing may lead to severe disruption of cognition. For example, recent preclinical and clinical findings indicate that such a regulatory impairment, leading to the $mGlu_5$ receptor-mediated excessive neuronal excitability, may be a critical component of fragile X syndrome, a major cause of mental retardation (Bear, 2005; Chuang et al., 2005).

Second, $mGlu_5$ receptor participates in synaptic plasticity mechanisms that serve as cellular substrates for learning and memory. To date, the involvement of $mGlu_5$ receptor in distinct forms of synaptic plasticity, including both long-term potentiation (LTP) and long-term depression (LTD), in several brain regions has been identified. In the hippocampus, the $mGlu_5$ receptor is critical for LTP induction, both in slice (Behnisch and Reymann, 1993; Camodeca et al., 1999; Jia et al., 1998; Lu et al., 1997; Neyman and Manahan-Vaughan, 2008) and in vivo preparations (Balschun and Wetzel, 2002; Bikbaev et al., 2008; Manahan-Vaughan and Braunewell, 2005; Naie and Manahan-Vaughan, 2004). Accordingly, the $mGlu_5$ receptor knockout mice show reduced hippocampal CA1 LTP in conjunction with impaired performance in cognitive tests (Lu et al., 1997). Repeated treatment with $mGlu_5$ receptor antagonist impairs working and spatial memory in correlation to the level of expression of the $mGlu_5$ receptor and impairment of hippocampal LTP (Manahan-Vaughan and Braunewell, 2005). The $mGlu_5$ receptor also plays a key role in the regulation of NMDA-independent LTD in hippocampus (Faas et al., 2002; Gasparini et al., 1999; Huang and Hsu, 2006; Huber et al., 2001). Notably, pathological imbalance between the $mGlu_5$ receptor-regulated hippocampal LTD and LTP may underlie cognitive impairment in fragile X syndrome (Bear et al., 2004; Huber et al., 2002; Lauterborn et al., 2007). In the lateral amygdala, the induction of LTP, and the subsequent formation of fear memories, are dependent on tonic $mGlu_5$ receptor activity (Fendt and Schmid, 2002; Rodrigues et al., 2002). In addition, a novel form of LTP has recently been identified in the neocortex that is independent of NMDA glutamate receptors and is predominantly mediated by the $mGlu_5$ receptor (Sourdet et al., 2003; Wang and Daw, 2003). This latter form of plasticity may have a key role in cognitive processing as suggested by observations that it is selectively deficient in fragile X mental retardation protein (FMRP)-knockout mice (Wilson and Cox, 2007), an experimental model for fragile X syndrome. The role of $mGlu_5$ receptor in synaptic plasticity may be mediated, at least in part, by its regulation of molecular mechanisms such as phosphorylation of extracellular signal-regulated protein kinase (ERK) 1/2 and transcription factor cAMP response element-binding (CREB) protein in hippocampus and prefrontal cortex (Liu et al., 2006, 2008; Mao et al., 2008). Regulation of these key pathways for learning and memory further supports the potential of the $mGlu_5$ receptor-based strategies for a procognitive effect.

In addition to the direct influence on synaptic excitability, *in vitro* studies have indicated that the $mGlu_5$ receptor activation plays a modulatory role by potentiating NMDA-evoked responses (Pisani et al., 1997). For example, in striatal slices, the selective $mGlu_5$ receptor agonist, (RS)-2-chloro-5-hydroxyphenylglycine (CHPG), potentiates the NMDA-induced membrane depolarization. This effect of CHPG is absent in slices that are pre-treated with the non-competitive $mGlu_5$ receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and in the $mGlu_5$ receptor knockout mice (Pisani et al., 2001). Likewise, the $mGlu_5$ receptor agonists enhance and antagonists attenuate the NMDA-evoked depolarizations in mice cortical wedges (Attucci et al., 2001). The $mGlu_5$ receptor is also involved in the potentiation of NMDA-induced currents in hippocampus (Doherty et al., 1997; Mannaioni et al., 2001). Together, these findings suggest that the $mGlu_5$ receptor may exert a positive interaction with NMDA receptor function. This interaction involves several components of intracellular signaling machinery including protein kinase C (Alagarsamy et al., 1999; Mao and Wang, 2002a,b), ERK (Yang et al., 2004), and CREB (Mao and Wang, 2002a). In addition, the positive functional interaction between the $mGlu_5$ and NMDA receptors also involves cross talk between their synaptic adaptor proteins, e.g. homer proteins, in the postsynaptic density (PSD) of neurons (Ango et al., 2000, 2001; Yang et al., 2004). The range of the $mGlu_5$ receptor effects on tonic firing activity, synaptic plasticity and NMDA receptor function suggest that these receptors may play an important role in maintaining the neuronal activity of the brain cognitive centers *in vivo*.

3. Electrophysiology of the $mGlu_5$ receptor blockers in awake animals

Notwithstanding the insights gained from *in vitro* studies, the nature of $mGlu_5$ receptor regulation of neuronal activity at the network level can be better understood by examining the tonically active and functionally connected brain of awake animals. Using *in vivo* single