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REVIEW

The possible involvement of metabotropic glutamate receptors in schizophrenia

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Abstract

Glutamate disruption is thought to have a major role in schizophrenia brain processes, possibly involving NMDA hypofunction. The metabotropic glutamate receptors are distributed in brain regions related to schizophrenia and seem to affect glutamate release in a moderate way. Compounds modulating these receptors are being investigated in animal models of schizophrenia, in an attempt to discover new antipsychotics. This article reviews the current research data regarding the role of these receptors in schizophrenia animal models. It was found that more research was done on Group I and II metabotropic receptors while investigation of group III receptors is still trailing behind. Accumulating evidence shows that mGluR5 antagonists by themselves do not necessarily disrupt pre-pulse inhibition (PPI), but can exacerbate disruption of PPI caused by MK-801 and PCP, while positive modulation of this receptor has beneficial effects on these models of psychosis. Group II agonists are also showing beneficial effects in animal models. It seems that metabotropic glutamate receptor modulators could be developed into a novel treatment of schizophrenia by altering glutamate release, thus overcoming the putative NMDA hypofunction. Although the implications from these pre-clinical studies to human schizophrenia patients are premature, the data obtained with some compounds point to promising results for drug development. More studies, with agents active at other mGluRs in animal models and schizophrenia patients as well as with human subjects are needed in order to clarify the role of the metabotropic glutamate receptors in the pathophysiology and pharmacotherapy of schizophrenia.

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1. Introduction

A large amount of investigation has gone into the possible role of glutamate, through its various receptorial systems, in the schizophrenia neuropathological process in the last decades. Most glutamatergic theories focus on the role of the *N*-Methyl-D-Aspartate (NMDA) receptor subtype. The main theory of glutamate involvement in schizophrenia suggests hypofunction of the NMDA subtype receptors (Olney and Farber, 1995; Olney et al., 1999; Farber, 2003) based on the psychotomimetic effect of non-competitive NMDA receptor antagonists such as MK-801 (Andine et al., 1999) or phencyclidine (PCP) (Javitt and Zukin, 1991) It was suggested that hypofunction of the NMDA receptor in the brain may be involved in the pathophysiology of schizophrenia. This theory led to clinical trials with several positive NMDA modulators, such as d-serine, cycloserine (Heresco-Levy et al., 2002) and glycine (Javitt et al., 1994), thus overcoming the putative NMDA hypofunction. Clinical trials with these compounds showed modest effect in schizophrenia. On the other hand, neural excitotoxicity due to excess of glutamate was suggested also to have a role in schizophrenia (Deutsch et al., 2001), thus contributing to the suggested neurodegenerative process of schizophrenia, again leading to the development of compounds aiming at antagonizing NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors, providing neuroprotection.

Psychosis is only one of the dimensions of schizophrenia phenomenology. Other signs of the schizophrenic process include the negative signs (anhedonia, avolition, flattening of affect), progressive functional cognitive decline and affective manifestations. Much of the pre-clinical research was confined to the "psychotic" dimension, while not addressing the other, debilitating clinical manifestations of schizophrenia. The human "psychotic" dimension refers to disturbances in the linearity and goal-directedness of thinking, hallucinations and delusions. However, what is often modeled are behaviors that relate to dopaminergic stimulation such as hyperlocomotion and stereotypies, whose relevance to productive psychotic symptoms is inferred, but, unfortunately, the "psychotic" dimension is not easily modeled with these "hard-wired" rodent behaviors.

Glutamate is the main excitatory neurotransmitter in the brain, and is involved in many complex processes related to cognition, memory and perception (Dingledine et al., 1999). Other important subtypes of the glutamate receptor seem to be relevant to the neuropathological infrastructure of schizophrenia, as well as are other psychiatric disorders, such as anxiety (Chavez-Noriega et al., 2002; Moghaddam, 2004). The objective of this article is to review the current research status, which is mainly pre-clinical, regarding the role of metabotropic glutamate subtype receptors in schizophrenia.

2. The metabotropic glutamate receptor subtype family

The glutamate receptor family is divided into ionotropic receptors which are oligomeric complexes forming a transmembranal ion channel, and metabotropic receptors which activate G-protein coupled intra-cellular metabolic processes (Kew and Kemp, 2005). NMDA, AMPA and Kainate ionotropic receptors, named after the agonist corresponding to their subtype, are mostly postsynaptic, expressed by nearly all subtypes of neurons. The NMDA receptor is mainly coupled to the Ca++ channel, while AMPA and kainate are mainly coupled to the Na+ channel (Dingledine et al., 1999). Glutamate binding to these receptors, results in fast excitatory neurotransmission, throughout the brain. Thus, manipulating the activity of these receptors may produce a global impact on brain function and produce profound side effects.

There are, currently, eight known metabotropic receptors (Table 1), named mGluR1-8, which are classified into three groups, Group I, II and III, according to their primary structure, second messenger coupling and pharmacological profile, (Conn and Pin, 1997). All the metabotropic receptors had been cloned and their genetic loci were identified. Group I includes mGluR1 and 5 and is predominantly coupled via Gq/G11 to phospholipase C. Group II, which includes mGluR1 and 3, and group III which includes mGluR4,6-8 are coupled via Gi/Go to inhibition of adenylyl cyclase activity. As a general rule these receptors exert a more modulatory role, regulating neuronal excitability, synaptic plasticity and neurotransmission. Metabotropic receptors, with the exception of mGluR6 which is confined primarily to the retina, are expressed in neuronal and glial cells, with specific distribution of each subtype. Neuronal group I mGluR is typically expressed postsynaptically in somatodendrityc domains while group II and III are predominantly presynaptic, localized in axonal domains and axon terminals where they regulate neurotransmitter release.

3. Methodology of preclinical research

Research data regarding the pharmacological effect of metabotropic glutamate receptor modulators is currently accumulating mainly from in vivo animal studies. Methods of research focused on knockout mice, receptor modulators and behavioral paradigms of

Table 1 Pharmacological properties of the mGluRs

	Group I	Group II	Group III
mGluR	1,5	2,3	4,6,7,8
G-protein Coupling	Gq/G11	Gi/Go	Gi/Go
2nd messenger	Inositol-3P	c-AMP	c-AMP
Synaptic localization	Post-synaptic	Pre-synaptic	Pre-synaptic
Brain localization	Hippocampus, amygdale, thalamus, ventral striatum, prefrontal cortex (mGluR1), nucleus accumbens and olfactory tubercle (mGluR5)	Cortex and dentate gyrus (mGluR2), thalamus, striatum, amygdale, hippocampus, glia (mGluR3)	Thalamus, retina (mGluR6)