Glutamate Receptor Abnormalities in Schizophrenia: Implications for Innovative Treatments

Maria D. Rubio, Jana B. Drummond and James H. Meador-Woodruff*

Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294-0021, USA

Abstract

Schizophrenia is a devastating psychiatric illness that afflicts 1% of the population worldwide, resulting in substantial impact to patients, their families, and health care delivery systems. For many years, schizophrenia has been felt to be associated with dysregulated dopaminergic neurotransmission as a key feature of the pathophysiology of the illness. Although numerous studies point to dopaminergic abnormalities in schizophrenia, dopamine dysfunction cannot completely account for all of the symptoms seen in schizophrenia, and dopamine-based treatments are often inadequate and can be associated with serious side effects. More recently, converging lines of evidence have suggested that there are abnormalities of glutamate transmission in schizophrenia. Glutamatergic neurotransmission involves numerous molecules that facilitate glutamate release, receptor activation, glutamate reuptake, and other synaptic activities. Evidence for glutamatergic abnormalities in schizophrenia primarily has implicated the NMDA and AMPA subtypes of the glutamate receptor. The expression of these receptors and other molecules associated with glutamate neurotransmission has been systematically studied in the brain in schizophrenia. These studies have generally revealed region- and molecule-specific changes in glutamate receptor transcript and protein expression in this illness. Given that glutamatergic neurotransmission has been implicated in the pathophysiology of schizophrenia, recent drug development efforts have targeted the glutamate system. Much effort to date has focused on modulation of the NMDA receptor, although more recently other glutamate receptors and transporters have been the targets of drug development. These efforts have been promising thus far, and ongoing efforts to develop additional drugs that modulate glutamatergic neurotransmission are underway that may hold the potential for novel classes of more effective treatments for this serious psychiatric illness.

Key Words: Ionotropic, Metabotropic, Antipsychotics, Modulators, Accessory proteins
refractory to treatment with antipsychotics. Consequently, alternative neurotransmitter systems that may be involved in the pathophysiology of schizophrenia have been sought.

A growing body of evidence now implicates glutamatergic dysfunction in schizophrenia. The most widely held hypothesis propose that schizophrenia is associated with decreased glutamate activity in limbic brain structures, likely involving the postsynaptic NMDA and/or AMPA subtypes of glutamate receptors (Itil et al., 1967; Aanonsen and Wilcox, 1986; Javitt and Zukin, 1991; Krystal et al., 1994; Coyle, 1996; Goff and Wine, 1997; Tammenga, 1999). Some of the most compelling evidence implicating glutamate dysfunction in schizophrenia is the fact that phencyclidine (PCP) and similar compounds, which are uncompetitive antagonists of the NMDA receptor, can induce both the positive and negative symptoms of schizophrenia, including cognitive deficits (Javitt and Zukin, 1991; Tammenga, 1999). Moreover, these compounds can exacerbate both positive and negative symptoms in schizophrenia (Lahti et al., 1995). Chronic administration of PCP-like compounds may provide a more valid model of schizophrenia than acute treatment, since it induces a persistent psychotic symptomatology (Javitt and Zukin, 1991), and reduces frontal lobe blood flow and glucose utilization, which is remarkably similar to the “hypofrontality” described in schizophrenia (Hertzmann et al., 1990). Acute PCP administration leads to decreased glutamate neurotransmission in the prefrontal cortex of rodents (Moghaddam et al., 1997; Moghaddam and Adams, 1998); however, relatively little is known of the impact of chronic PCP exposure on the glutamate system. Electrophysiological data show heightened depolarization of prefrontal cortical pyramidal neurons of rats chronically treated with PCP following local application of NMDA (Arvanov and Wang, 1999; Yu et al., 2002). Chronic PCP treatment alters expression of NMDA receptor subunits, as well as the subunit stoichiometry of the NMDA receptor (Yu et al., 2002). A possible interpretation of these data is that chronic PCP treatment leads to a prolonged reduction in glutamate transmission, resulting in increased NMDA receptor expression and an amplified response to exogenous NMDA application (Jentsch and Roth, 1999). These observations, taken together, suggest that glutamatergic abnormalities in schizophrenia likely involve the NMDA receptor or its downstream signaling pathways. Given that NMDA receptor firing requires partial predepolarization of the postsynaptic membrane by activation of AMPA receptors, abnormal AMPA receptor expression or function may be manifested as an NMDA receptor abnormality. Accordingly, the AMPA receptor has also been implicated in the pathophysiology of this illness.

As candidate genes associated with neurotransmission have been sought as possible substrates for aspects of the pathophysiology of schizophrenia, a number of proteins and pathways have been identified. A high level of complexity of the cell biology of neurotransmission is recognized, resulting in numerous candidate genes for involvement in schizophrenia. Neurotransmission involves myriad molecules, including presynaptic and postsynaptic receptors; intracellular receptor-interacting proteins that link receptors to signal transduction pathways; cytoskeletal elements, and other receptors; signal transduction cascades; membrane- and vesicle-bound transporters; synthetic and catabolic enzymes; and machinery that regulates expression of all of these molecules at both transcriptional and translational levels. To further appreciate the role that glutamate may have in the pathophysiology of schizophrenia, and the potential molecular targets for new drug discovery, we briefly review the physiology of glutamatergic transmission.

**GLUTAMATERGIC NEUROTRANSMISSION**

The tripartite glutamatergic synapse is characterized by bidirectional communications between the pre-synaptic neuron, the post-synaptic neuron and the surrounding astrocytes (Araque et al., 1999; Ni et al., 2007). Initially, glutamate is synthesized from glutamine in the presynaptic neuron, where it is packaged into secretory vesicles by one of at least three vesicular glutamate transporters (VGLUT 1-3) (Aihara et al., 2000; Bellocchio et al., 2000; Takamori et al., 2000; Fremeau et al., 2002). Upon excitation of the pre-synaptic neuron, the glutamatergic vesicles fuse with the pre-synaptic membrane and release their contents into the synaptic cleft. Synaptic glutamate then acts upon different glutamatergic receptors in the pre- and post-synaptic membranes and on astrocytes (Kanai et al., 1993; Masson et al., 1999; Danbolt, 2001). The rapid clearance of extracellular glutamate is mediated by high affinity membrane excitatory amino acid transporters (EAAT1-EAAT5), located on both neurons and astrocytes (Kanai et al., 1993; Rothstein et al., 1994; Lehr et al., 1995; Bar-Peled et al., 1997; Milton et al., 1997; Nagao et al., 1997; Gesemann et al., 2010; Neuhausen et al., 2010; Rico et al., 2010). Recovered glutamate in astrocytes either enters the TCA cycle as α-ketoglutarate, or is converted into glutamine by glutamine synthetase. Glutamine is then released from astrocytes for uptake into the pre-synaptic neuron (Danbolt, 2001). In this neuron, the enzyme glutaminase can oxidize glutamine into glutamate, which is then repackaged into vesicles for its subsequent release (Danbolt, 2001) (Fig. 1).

Once released into the synaptic cleft, glutamate acts upon glutamate receptors. These include ionotropic glutamate receptors, which are ligand-gated ion channels (NMDA, AMPA and kainate subtypes, Table 1) that mediate fast excitatory transmission, and G-protein coupled metabotropic receptors (mGlurR1-8, Table 2) responsible for modulating and fine tuning the synapse (Hollmann and Heinemann, 1994; Bleakman and Lodge, 1998).

**NMDA receptors**

NMDA receptors (Table 1) are heterotetramers composed of two obligatory GluN1 subunit and two regulatory GluN2 or GluN3 subunits (Collingridge et al., 2009). GluN1 is alternatively spliced into eight forms while four different genes encode for GluN2 (GluN2A-D) and two genes encode for GluN3 (GluN3A-B). The properties and localization of the NMDA receptor vary according to the subunit composition of the channel. The typical NMDA receptor is composed of a dimer of GluN1 and a dimer of GluN2 subunits that have glycine and glutamate binding properties, respectively. Receptors containing two GluN1 and two GluN3 subunits, on the other hand, only bind glycine and their activity is independent from glutamate. The subunit composition of NMDA receptors not only differs within areas of the human brain and in different stages of development, but also within synaptic regions (Rao and Craig, 1997; Thomas et al., 2006). GluN1/2A, for example, predominates in adult synaptic sites while GluN1/2B is more abundant in extrasynaptic sites during development (Cull-Candy et al., 2001).