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Glutamate Receptor Abnormalities in Schizophrenia: Implications for Innovative Treatments

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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

Schizophrenia is a devastating illness that afflicts 1% of the population, or more than 60 million people worldwide. This is one of the most serious of all psychiatric illnesses: more hospital beds (psychiatric and medical combined) are filled by persons with schizophrenia than due to any other medical condition (Buchanan and Carpenter, 2000). This disorder is characterized by a constellation of clinical findings, often divided into positive and negative symptoms. Positive symptoms include dramatic hallucinations, which are often auditory. Patients report that they hear voices that are clearly located outside of their heads, most often engaged in a running commentary on their thoughts and behaviors. Other common positive symptoms include paranoid delusions and disorders of thought processes. Much more insidious and debilitating are the negative symptoms, which are associated with the diminution of normal social behaviors, and include withdrawal, decreased spontaneous communication, decreased eye contact, decreased or muted facial expression and vocal inflection, and diminished spontaneous movement (Buchanan and Carpenter, 2000).

For decades, schizophrenia research focused on the dopamine hypothesis of schizophrenia, which postulates that dysregulated dopaminergic neurotransmission is a key feature of the pathophysiology of the illness. The dopamine hypothesis is based on the observation that antipsychotics block D_2 receptors, and their affinity for these receptors highly correlates with their ability to ameliorate some psychotic symptoms. Second, psychostimulants that enhance dopaminergic activity can elicit positive symptoms of schizophrenia, including delusions, hallucinations, and thought disorder. Although numerous studies point to dopaminergic abnormalities in schizophrenia (Joyce and Meador-Woodruff, 1997; Laruelle *et al*., 1999), dopamine dysfunction cannot completely account for all of the symptoms seen in schizophrenia, since neuroleptics typically are effective only for the positive symptoms of the illness, while negative symptoms and cognitive deficits are relatively

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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; Tamminga, 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; Tamminga, 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 increased 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 pre- and post- synaptic 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; Lehre *et al.*, 1995; Bar-Peled *et al.*, 1997; Milton *et al.*, 1997; Nagao *et al.*, 1997; Gesemann *et al.*, 2010; Neuhauss *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 synthethase. 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 (mGluR1-8, 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).

NMDA receptor subunits are synthesized in the endoplasmic reticulum (ER), where they assemble into heterotetramers. GluN1/2 and 1/3 complexes exit the ER, are modified in the Golgi apparatus and sorted in the trans-Golgi network (TGN). The mature complexes leave the TGN packaged into vesicles that are either delivered to the cell surface or to endosomes. NMDA receptor vesicles are initially trafficked on microtubules by KIF17 (protein kinesin family member 17) and delivered to the dendritic spine surface membrane in a later stage by myosin cargo proteins sliding on actin filaments (Lau and Zukin, 2007; Stephenson *et al.*, 2008). At the synaptic site, there is subunit specific recycling which also contributes to the pool of available receptors (Lavezzari *et al.*, 2004).

NMDA receptors form large complexes with intracellular proteins that regulate their trafficking, delivery and anchoring to the synapse (Sans *et al.*, 2003; Prybylowski *et al.*, 2005; Sans *et al.*, 2005). These proteins link the receptors to the underlying cytoskeletal machinery and allow the activation of downstream molecular pathways. Intracellular proteins bind to the C-terminus of specific subunits. GluN1, for example, is phosphorylated on its C-terminus by PKA and PKC and this modulation promotes NMDA receptor trafficking to the membrane (Tingley *et al.*, 1993; Tingley *et al.*, 1997; Chung *et al.*, 2004). GluN2, on the other hand, is phosphorylated by Fyn, an event that prevents the receptor's endocytosis from the synapse (Sala and Sheng, 1999). The membrane associated guanylate kinase (MAGUK) family of scaffolding proteins is involved in the trafficking and clustering of GluN2 subunits. This family includes chapsyn-110, postsynaptic density (PSD) -95, PSD-93, synapse associated protein (SAP) 97 and SAP102.

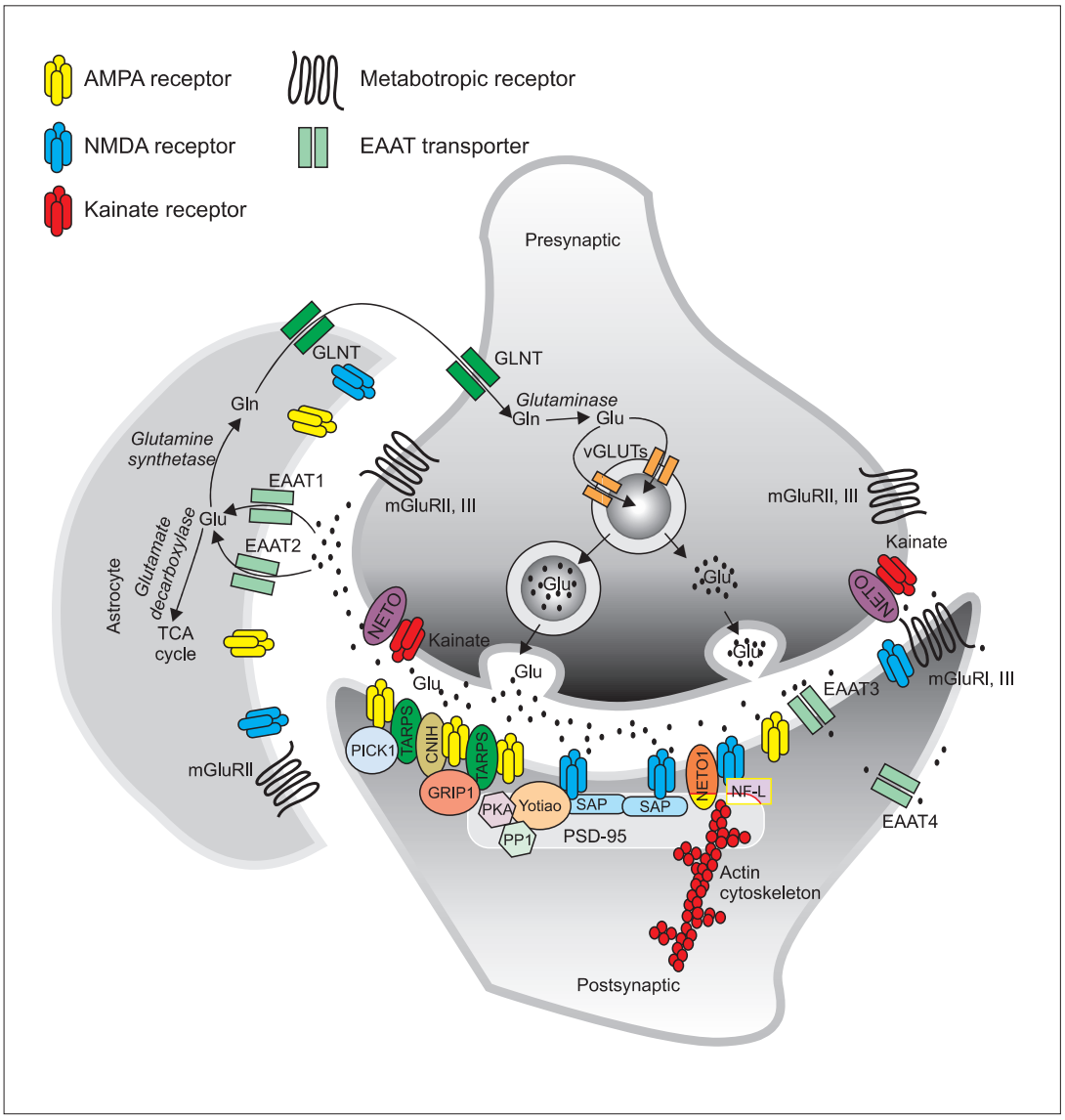

Fig. 1. The glutamatergic synapse. Glutamate is packaged into presynaptic vesicles and released to the synaptic cleft where it acts upon ionotropic and metabotropic receptors and is rapidly cleared by EAATs. In the astrocyte, glutamate either enters the TCA cycle or is converted to glutamine by the enzyme glutamine synthetase. Glutamine is then released to the presynaptic neuron where it is converted to glutamate and packaged into vesicles for further release.

Table 1. Classification and features of ionotropic glutamate receptors

Family	Subunit*	Characteristics	Alternative nomenclature*
NMDA	GluN1	- Glycine binding - Obligatory subunit	GLU_{N1}, NMDA-R1, NR1, GluRζ1
	GluN2A	- Glutamate binding - Primarily synaptic - Ubiquitous expression in adult brain - High channel conductance - High sensitivity to Mg^{2+}	GLU_{N2A}, NMDA-R2A, NR2A, GluRε1
	GluN2B	- Glutamate and polyamine binding - Primarily extrasynaptic - Highly expressed in early development - Primarily expressed in adult forebrain - High channel conductance - High sensitivity to Mg^{2+}	GLU_{N2B}, NMDA-R2B, NR2B, hNR3, GluRε2
	GluN2C	- Glutamate binding - Primarily expressed in adult cerebellum - Low channel conductance - Low sensitivity to Mg^{2+}	GLU_{N2C}, NMDA-R2C, NR2C, GluRε3
	GluN2D	- Glutamate binding - Primarily extrasynaptic - Highly expressed in early development - Low channel conductance - Low sensitivity to Mg^{2+}	GLU_{N2D}, NMDA-R2D, NR2D, GluRε4
	GluN3A	- Glycine binding - Primarily extrasynaptic - Highly expressed in early development - Low channel conductance - Low sensitivity to Mg^{2+}	GLU_{N3A}, NMDA-R3A, NMDAR-L, chi-1
	GluN3B	- Glycine binding - Primarily extrasynaptic - Highly expressed in the spinal cord, pons, midbrain and medulla. - Low channel conductance - Low sensitivity to Mg^{2+}	GLU_{N3B}, NMDA-R3B
AMPA	GluA1	- Ca^{2+} permeable - Impermeable when coupled to edited GluA2 - Higher conductance	Glu_{A1},GluR1, GluRA, GluR-A, GluR-K1, HBGR1
	GluA2	- Q/R edited: Linear current–voltage relationship Impermeable to Ca^{2+} Low single-channel conductance - Q/R unedited: Inwardly rectifying when blocked by endogenous intracellular polyamines Ca^{2+} permeable Higher conductance	Glu_{A2},GluR2, GluRB, GluR-B, GluR-K2, HBGR2
	GluA3	- Ca^{2+} permeable - Impermeable when coupled to edited GluA2 - Higher conductance	GLU_{A3}, GluR3, GluRC, GluR-C, GluR-K3
	GluA4	- Ca^{2+} permeable - Impermeable when coupled to edited GluA2 - Higher conductance	GLU_{A4}, GluR4, GluRD, GluR-D

Table 1. Continued

Family	Subunit*	Characteristics	Alternative Nomenclature*
Kainate	GluK1	- Can form homomeric channels - Required for functional heteromeric receptors - Found in cortex, striatum, hippocampus, dorsal root ganglia and cerebellum. - Q/R edited: Linear current–voltage relationship Impermeable to Ca^{2+} Low single-channel conductance - Q/R unedited: Inwardly rectifying when blocked by endogenous intracellular polyamines Ca^{2+} permeable Higher conductance	GLU_{K5}, GluR5, GluR-5, EAA3
	GluK2	- Can form homomeric channels - Required for functional heteromeric receptors - Found in cortex, striatum, hippocampus, dorsal root ganglia, retina and cerebellum - Q/R edited: Linear current–voltage relationship Impermeable to Ca^{2+} Low single-channel conductance - Q/R unedited: Inwardly rectifying when blocked by endogenous intracellular polyamines Ca^{2+} permeable Higher conductance	GLU_{K6}, GluR6, GluR-6, EAA4
	GluK3	- Can form homomeric channels - Required for functional heteromeric receptors - Found in cortex, hippocampus, retina and cerebellum.	GLU_{K7}, GluR7, GluR-7, EAA5
	GluK4	- Only forms heteromeric receptors - Primarily located at hippocampal CA3 and dentate granule neurons and purkinje cells in cerebellum	GLU_{K1}, KA1, KA-1, EAA1
	GluK5	- Only forms heteromeric receptors - Found in cortex, hippocampus, retina and cerebellum.	GLU_{K2}, KA2, KA-2, EAA2

*Collingridge *et al.*, 2009.

Each of these proteins differentially interact with and modulate specific GluN2 isoforms (Cousins *et al.*, 2008). Another novel auxiliary protein, neuropilin tolloid-like 1 (NETO1), is thought to be involved in maintenance and/or insertion of GluN2A NMDA receptors at the synapse of the CA1 region of the hippocampus (Ng *et al.*, 2009). Two intracellular proteins that interact with the GluN1 subunit have been described to date: the neuronal intermediate filament protein, neurofilament-light (NF-L) that prevents ubiquitination and subsequent degradation of GluN1 (Ehlers *et al.*, 1998; Ratnam and Teichberg, 2005), and Yotiao (Lin *et al.*, 1998) that regulates channel activity by linking NMDA receptors to PKA and PP1 (Westphal *et al.*, 1999).

Because of the well-established role of NMDA receptors in neurotoxicity and synaptic plasticity, novel drugs primarily target NMDA receptor modulation through interactions at the glycine binding co-agonist site of this receptor. However, NMDA receptor synthesis, trafficking delivery and anchoring to the synaptic site involves a large number of molecules that have recently been identified and characterized. All of these molecules are potential sites for drug development to treat the symptoms of schizophrenia.

AMPA receptors

Similar to NMDA receptors, AMPA-type glutamate receptors (Table 1) are involved in fast glutamate transmission, neuronal circuit remodeling and higher order cognitive functions such as learning and memory (Malinow and Malenka, 2002; Kessels and Malinow, 2009; Keifer and Zheng, 2010). AMPA receptors are homotetramers assembled as dimers of GluA subunits dimers (Collingridge *et al.*, 2009; Sobolevsky *et al.*, 2009). GluA subunits 1-4 are encoded by independent genes (Boulter *et al.*, 1990; Keinanen *et al.*, 1990) and assemble into homodimers in the ER, where they undergo conformational changes necessary for the proper function of the receptors

Table 2. Classification and features of metabotropic glutamate receptors

Family and Receptors	Coupling	Characteristics
Group I	Excitatory	
mGluR1	G_q coupled	- Primarily postsynaptic - Expressed in neurons
mGluR5	G_q coupled	- Primarily postsynaptic - Expressed in neurons and astrocytes
Group II	Inhibitory	
mGluR2	G_i coupled	- Primarily presynaptic - Expressed in neurons and astrocytes
mGluR3	G_i coupled	- Pre- and postsynaptic - Expressed in neurons and astrocytes
Group III	Inhibitory	
mGluR4	G_i coupled	- Pre- and postsynaptic - Expressed in neurons and reactive astrocytes
mGluR6	G_i coupled	- Exclusively in postsynapses of retinal bipolar metabotropic (ON-center) cells
mGluR7	G_i coupled	- Pre- and postsynapses - Expressed in neurons
mGluR8	G_i coupled	- Primarily presynaptic - Expressed in neurons and reactive astrocytes

and quality control of folding and dimerization (Mah *et al.*, 2005). Further post translational modifications of AMPA receptor subunits occur in the Golgi apparatus, involving phosphorylation and glycosylation (Greger and Esteban, 2007). The cellular and subcellular localization and biophysical properties of the different AMPA receptors vary according to their subunit composition (Hayashi *et al.*, 2000; Shi *et al.*, 2001). The GluA1 subunit, for example, is required for trafficking of receptors in response to activity and participates in basal neurotransmission, while the GluA2 subunit participates in basal conditions regulating Ca^{2+} permeability, homeostasis, and trafficking to the synapse (Granger *et al.*, 2011).

AMPA receptor subunits contain specific PDZ-binding domains on their cytoplasmic carboxy-termini (C-termini) consisting of approximately 90 amino acids. These domains enable their interactions with other PDZ-containing intracellular proteins within the postsynaptic density (PSD), which are important for AMPA receptor expression, function and localization within the cell (Malinow and Malenka, 2002). PDZ interactions occurring between the C-termini of AMPA receptor subunits and accessory PSD proteins such as PICK1, involved in GluA2 sorting and recycling (Steiner *et al.*, 2005), and GRIP1, which regulates trafficking, anchoring and endocytosis of AMPA receptors (Citri *et al.*, 2010; Clem *et al.*, 2010; Anggono *et al.*, 2011), can facilitate specific patterns of AMPA receptor trafficking to the PSD (Malinow and Malenka, 2002). Similarly, these domains enable AMPA receptors to colocalize with NMDA receptors at the synaptic membrane via anchoring proteins such as the SAP family proteins, or have their recycling pool regulated by another accessory protein, NSF (Song *et al.*, 1998; Chen *et al.*, 2000).

Another AMPA receptor modulatory protein, transmembrane AMPA regulatory protein 2 (TARP2, or stargazin), was the first transmembrane protein found to interact with AMPA receptors (Chen *et al.*, 2000; Diaz, 2010). TARP2 was first identified in the naturally occurring mutant stargazer mouse that lacks functional AMPA receptors at cerebellar granule cell synapses (Noebels *et al.*, 1990; Letts *et al.*, 1998; Hashimoto *et al.*, 1999; Chen *et al.*, 2000). TARP2 is a member of a family of eight closely related AMPA receptor auxiliary proteins that are widely expressed in the brain and share homology with the γ-1 accessory subunit of the voltage dependent calcium channels found in skeletal muscle. TARPs have biophysical effects on AMPA receptors, such as controlling channel gating, kinetics, glutamate binding affinity, activation and desensitization rates, and receptor stability (Tomita, 2010). Class I TARPS, (TARP2, 3, 4 and 8) and Class II TARPs (TARP5 and 7) have distinct properties. The members of Class I have slow deactivation and desensitization rates, increase glutamate and kainate efficacy, and increase steady-state currents and receptor trafficking (Kato *et al.*, 2010). TARP7 also decreases deactivation kinetics and increases kainate efficacy and steady-state currents, but has been shown to have less effect on glutamate affinity or receptor trafficking (Kato *et al.*, 2010). TARP5 shows even more differences, and has been reported to increase deactivation, decrease glutamate affinity and steady-state current, and have little effect on kainate efficacy and receptor trafficking (Kato *et al.*, 2010).

AMPA receptors and TARPs are coassembled in the ER, and it is here that they form their first direct interaction (Coombs and Cull-Candy, 2009; Tomita, 2010). After assembly, the AMPA receptor/TARP complex is trafficked through the Golgi apparatus and to the synaptic membrane before being laterally translocated to the PSD (Bredt and Nicoll, 2003; Beneyto and Meador-Woodruff, 2006; Coombs and Cull-Candy, 2009). At the PSD, the PDZ domain of the TARP protein binds to the PDZ domain of a PSD scaffolding protein, PSD-95, anchoring the complex to the membrane (Chen *et al.*, 2000; Chen *et al.*, 2003; Bats *et al.*, 2007). AMPA receptors cannot bind directly to PSD-95, and rely on TARP proteins to provide this important structural role for AMPA receptor stability (Tomita, 2010).

The cornichon protein family has also been recently identi-

fied as auxiliary proteins of AMPA receptors that have similar functions to TARPs. CNIH2 and CNIH3 are coassembled with an estimated 70% of native AMPA receptors in the rat brain, and have been shown to enhance surface expression and gating of AMPA receptors (Schwenk *et al.*, 2009). As with the TARPs, cornichons have also been reported to slow deactivation and desensitization of AMPA receptors (Schwenk *et al.*, 2009).

AMPA receptors may be coassembled with both TARPs and cornichons. Additionally, there are other AMPA receptors accessory molecules that bind to AMPA receptors or that complex with TARPs and cornichons to affect the trafficking and kinetics of these receptors. The cystine-knot AMPA receptor modulating protein (CKAMP44) associates with TARP-associated AMPA receptors in synaptic spines and increases their deactivation and desensitization (von Engelhardt *et al.*, 2010). SynDIG1, or synapse differentiation induced gene 1, has recently been shown to regulate the development of excitatory synapses and is colocalized with AMPA receptors in heterologous cells (Kalashnikova *et al.*, 2010). Similarly, NARP, EphB2 and SALM2 are other molecules known to be involved with targeting AMPA receptors to the developing excitatory synapse, and nPIST, a Golgi protein, promotes AMPA receptor clustering and may be important for AMPA receptor trafficking to the plasma membrane (Cuadra *et al.*, 2004; Kalashnikova *et al.*, 2010).

Kainate receptors

Different from other ionotropic receptors, kainate receptors (Table 1) show strong desensitization kinetics and slow response recovery (Lerma, 2003), serve primarily a modulatory function at the synapse, and are predominantly located presynaptically throughout the brain. Kainate receptors subunits 1-5 (GluK1-5) are encoded by different genes and undergo alternative splicing. GluK1-3 can form functional homomeric ion channels and are required for functional heteromeric receptors. In contrast, GluK4 and 5 are not able to form homomeric channels but do assemble with GluK1-3 into functional heteromeric receptor complexes (Bettler *et al.*, 1990; Egebjerg *et al.*, 1991; Schiffer *et al.*, 1997). The kinetics properties

Table 3. Glutamate receptor abnormalities in schizophrenia versus comparison subjects

Family	Subunit	Cortex		Hippocampus		Thalamus		B. G.	
		T	P	T	P	T	P	T	P
NMDA	GluN1	$\downarrow^{1\text{-}3}/\uparrow^{4,5}/\leftrightarrow^{6}$	$\uparrow/^{7}\leftrightarrow^{8}$	$\downarrow^{9}/\leftrightarrow^{6}$	$\downarrow^{10}$	$\downarrow^{11,12}/\leftrightarrow^{13,14}$	$\leftrightarrow^{15}$	$\leftrightarrow^{16}/\uparrow^{17}$	
	GluN2A	$\uparrow^{4}/\downarrow^{3}/\leftrightarrow^{6}$	$\leftrightarrow^{7}$	$\leftrightarrow^{6,9}$		$\leftrightarrow^{11,13,14}$	$\leftrightarrow^{15}$	$\leftrightarrow^{16}/\uparrow^{17}$	
	GluN2B	$\leftrightarrow^{3,6,18}$	$\leftrightarrow^{7}/\downarrow^{8}$	$\uparrow^{9}/\leftrightarrow^{6}$		$\uparrow^{14}/\downarrow^{11}/\leftrightarrow^{13}$	$\uparrow^{15}$	$\leftrightarrow^{16}/\uparrow^{17}$	
	GluN2C	$\downarrow^{3}/\leftrightarrow^{6,18}$	$\leftrightarrow^{7}$	$\leftrightarrow^{6}$		$\downarrow^{11}/\leftrightarrow^{13,14}$		$\leftrightarrow^{16}/\uparrow^{17}$	
	GluN2D	$\uparrow^{18}/\leftrightarrow^{3,6}$	$\leftrightarrow^{7}$	$\leftrightarrow^{6}$		$\leftrightarrow^{11,13,14}/\downarrow^{19}$		$\leftrightarrow^{16}/\uparrow^{17}$	
	GluN3A	$\uparrow^{20}$							
AMPA	GluA1	$\downarrow^{1}/\uparrow^{21}/\leftrightarrow^{3,6}$	$\uparrow^{22}/\downarrow^{23}$	$\downarrow^{24,25}/\leftrightarrow^{6}$	$\downarrow^{26}/\leftrightarrow^{27}$	$\downarrow^{11}/\leftrightarrow^{13}$		$\leftrightarrow^{16}/\uparrow^{17}$	
	GluA2	$\downarrow^{28}/\uparrow^{18}/\leftrightarrow^{6,21}$	$\downarrow^{23}/\leftrightarrow^{27}$	$\downarrow^{25,29}/\leftrightarrow^{6}$	$\downarrow^{25,26}/\leftrightarrow^{27}$	$\leftrightarrow^{11,13}$		$\leftrightarrow^{16}/\uparrow^{17}$	
	GluA3	$\leftrightarrow^{6,21,28}$	$\leftrightarrow^{27}$	$\leftrightarrow^{6}$	$\downarrow^{26}/\leftrightarrow^{27}$	$\downarrow^{11,19}/\leftrightarrow^{13}$		$\leftrightarrow^{16}/\uparrow^{17}$	
	GluA4	$\downarrow^{28}/\uparrow^{21}/\leftrightarrow^{6}$		$\leftrightarrow^{6}$		$\leftrightarrow^{11}$		$\leftrightarrow^{16}/\uparrow^{17}$	
Kainate	GluK1	$\downarrow^{6,30}/\leftrightarrow^{31}$		$\leftrightarrow^{6}$	$\downarrow^{32}/\leftrightarrow^{27}$	$\leftrightarrow^{11,13}$		$\leftrightarrow^{16,31}/\uparrow^{17}$	
	GluK2	$\leftrightarrow^{6,31}$		$\downarrow^{33}/\leftrightarrow^{6}$	$\downarrow^{32}$	$\downarrow^{19}/\leftrightarrow^{13}$		$\leftrightarrow^{16,17,31}$	
	GluK3	$\uparrow^{31}/\downarrow^{1}/\leftrightarrow^{6}$		$\leftrightarrow^{6}$	$\downarrow^{32}$	$\downarrow^{19}/\leftrightarrow^{13}$		$\leftrightarrow^{16,17,31}$	
	GluK4	$\downarrow^{1}/\leftrightarrow^{6,31}$		$\leftrightarrow^{6}$		$\leftrightarrow^{11}$		$\leftrightarrow^{16,17,31}$	
	GluK5	$\downarrow^{31}/\leftrightarrow^{6}$		$\downarrow^{33}/\leftrightarrow^{6}$		$\downarrow^{11}/\leftrightarrow^{13}$		$\leftrightarrow^{16,17,31}$	
mGluR	mGluR1	$\uparrow^{34}$	$\uparrow^{35}$			$\leftrightarrow^{11,36}$			$\leftrightarrow^{35}$
	mGluR2	$\uparrow^{37}/\downarrow^{38}$	$\uparrow^{35}/\leftrightarrow^{39,40}$			$\leftrightarrow^{11,36}$			$\leftrightarrow^{35}$
	mGluR3	$\leftrightarrow^{41}$	$\uparrow^{35}/\downarrow^{39}$			$\leftrightarrow^{11,36}$			$\leftrightarrow^{35}$
	mGluR4		$\leftrightarrow^{35}$			$\leftrightarrow^{11,36}$			$\leftrightarrow^{35}$
	mGluR5	$\uparrow^{41}/\leftrightarrow^{34}$	$\leftrightarrow^{35}$			$\leftrightarrow^{11,36}$			$\leftrightarrow^{35}$
	mGluR6					$\leftrightarrow^{11}$			
	mGluR7					$\leftrightarrow^{11,36}$			
	mGluR8					$\leftrightarrow^{11,36}$			

T: Transcript, P: Protein, B. G.: Basal ganglia, ↑: increased, ↓: decreased, ↔: unchanged. [1]Sokolov, 1998; [2]Humphries *et al.*, 1996; [3]Beneyto and Meador-Woodruff, 2008; [4]Dracheva *et al.*, 2001; [5]Le Corre *et al.*, 2000; [6]Beneyto *et al.*, 2007; [7]Kristiansen *et al.*, 2006; [8]Kristiansen *et al.*, 2010a; [9]Gao *et al.*, 2000; [10]Vrajova *et al.*, 2010; [11]Ibrahim *et al.*, 2000; [12]Clinton *et al.*, 2003; [13]Dracheva *et al.*, 2008; [14]Clinton and Meador-Woodruff, 2004; [15]Clinton *et al.*, 2006; [16]Meador-Woodruff *et al.*, 2001a; [17]Mueller *et al.*, 2004; [18]Akbarian *et al.*, 1996; [19]Sodhi *et al.*, 2011; [20]Mueller and Meador-Woodruff, 2004; [21]Dracheva *et al.*, 2005; [22]Hammond *et al.*, 2010; [23]Corti *et al.*, 2011; [24]Harrison *et al.*, 1991; [25]Eastwood *et al.*, 1995; [26]Eastwood *et al.*, 1997a; [27]Breese *et al.*, 1995; [28]Beneyto and Meador-Woodruff, 2006; [29]Eastwood *et al.*, 1997a; [30]Scarr *et al.*, 2005; [31]Meador-Woodruff *et al.*, 2001a; [32]Benes *et al.*, 2001; [33]Porter *et al.*, 1997; [34]Volk *et al.*, 2010; [35]Gupta, *et al.*, 2005; [36]Richardson-Burns *et al.*, 2000; [37]Ghose *et al.*, 2009; [38]Gonzalez-Maeso *et al.*, 2008; [39]Ghose *et al.*, 2008; [40]Crook *et al.*, 2002; [41]Ohnuma *et al.*, 1998.

of kainate receptors vary according to their subunit composition, localization and developmental stage. Several accessory subunits have been recently identified for kainate receptors. Among them, NETO1 has been characterized as an auxiliary protein participating in both kainate and NMDA receptor regulation (Ng *et al.*, 2009; Copits *et al.*, 2011; Straub *et al.*, 2011; Tang *et al.*, 2011). While NETO1 controls kainate receptor current kinetics, NETO2 drives receptor insertion into the plasma membrane, targets GluK1 receptors to the synapse, and significantly reduces receptor desensitization to glutamate (Zhang *et al.*, 2009; Copits *et al.*, 2011; Straub *et al.*, 2011). Because NETO proteins regulate kainate receptor activity and localization, they are potential targets for drug discovery.

Metabotropic glutamate receptors

The eight metabotropic glutamate receptors (mGluRs) members are divided into three groups (group I [mGluR1 and 5], group II [mGluR2 and 3] and group III [mGluR4, 6, 7, 8]), based on their pharmacological properties and the nature of their downstream signaling pathways (Table 2). Group I mGluRs are primarily localized on postsynaptic membranes, often close to NMDA receptors and modulating their activity. They activate $G\alpha_q$ proteins, resulting in increased intracellular calcium levels. Presynaptic group II and III receptors activate $G\alpha_i$, decreasing cAMP levels and modulating presynaptic glutamate release (Schoepp, 2001). Different mGluRs have unique regional and subcellular localization, as well as specific positive and negative modulators (Olive, 2009) (Table 2). Recently, drugs targeted towards group II mGluRs have proven successful in early stage clinical trials in schizophrenia as discussed below.

RECEPTOR ABNORMALITIES IN SCHIZOPHRENIA

Recent postmortem brain studies have found alterations of ionotropic glutamate receptors (NMDA, AMPA, and kainate, Table 3) and metabotropic glutamate receptors in schizophrenia. Accordingly, these pharmacologically distinct receptors have become targets for new drug discovery. Changes in subunit expression and binding sites in schizophrenia appear to be specific to limbic, cortical and hippocampal brain regions and have been interpreted to suggest abnormal subunit stoichiometry of glutamate receptors. Examination of glutamate receptor accessory molecules has revealed robust changes in their expression levels in schizophrenia as well, suggesting that regulation of glutamatergic neurotransmission and intracellular signaling is compromised in this illness.

NMDA receptors

Converging evidence suggests decreased function of NMDA receptors in schizophrenia, which has resulted in numerous studies examining NMDA receptor expression in this illness (Table 3). Conflicting findings have been reported in different cortical regions. In the prefrontal cortex, transcript studies found increased GluN2D and decreased GluN2C subunit expression (Akbarian *et al.*, 1996). In the dorsolateral prefrontal cortex (DLPFC), studies have reported both increased GluN1 and GluN3A transcript expression (Mueller and Meador-Woodruff, 2004; Dracheva *et al.*, 2008) and decreased GluN1, GluN2A and GluN2C expression (Beneyto and Meador-Woodruff, 2008). Relatively fewer changes have been noted when proteins rather than transcripts have been studied in this area. Total cell homogenates and autoradiography studies found no differences in NMDA receptor subunit expression in the DLPFC, but when ER subfractions were studied, a selective decrease of GluN2B expression was found (Beneyto and Meador-Woodruff, 2008; Kristiansen *et al.*, 2010a). In the anterior cingulated cortex (ACC), increased NMDA binding and increased protein expression of the GluN1-C2′ GluN1 isoform was found (Zavitsanou *et al.*, 2002; Kristiansen *et al.*, 2006). A selective increase of NMDA receptor binding was found in the posterior cingulate cortex (Newell *et al.*, 2005). In the occipital cortex, increased GluN1 and GluN2A subunit transcripts have been reported (Humphries *et al.*, 1996; Sokolov, 1998; Le Corre *et al.*, 2000; Dracheva *et al.*, 2001). In the cerebellum, findings vary with polymorphisms of the neuregulin (*NRG*) gene. Gene expression of the GluN2D subunit was increased in the cerebellum of homozygous patients, while GluN2C subunit expression was decreased in patients with a *NRG* polymorphism (Schmitt *et al.*, 2010).

In the hippocampal region, reduced MK801 binding suggested NMDA receptor abnormalities in schizophrenia (Beneyto *et al.*, 2007). Supporting this, a study on pan and isoform specific GluN1 proteins reported decreased in total GluN1 and GluN1-4b isoform expression in the left hippocampus, and of the GluN1-2b isoform in the right hippocampus (Vrajova *et al.*, 2010). Another study, focused on the identification of receptor transcript abnormalities in hippocampal subregions, found a selective decrease in GluN1 transcripts in the dentate gyrus in schizophrenia, and increased GluN2B transcripts in the CA2 area (Gao *et al.*, 2000). These transcript data, however, conflict with other studies that show no change in GluN1 and GluN2 isoforms in hippocampal subregions in this illness (McCullumsmith *et al.*, 2007). These data suggest the possibility of region and isoform specific GluN abnormalities in the hippocampus in schizophrenia.

Contradictory findings have been reported in the thalamus. GluN1 transcript has been reported to be decreased or unchanged, while GluN1 protein expression was found unchanged (Ibrahim *et al.*, 2000; Clinton and Meador-Woodruff, 2004; Clinton *et al.*, 2006). Similarly, GluN2B transcripts were reported to be decreased or increased in schizophrenia (Ibrahim *et al.*, 2000; Clinton and Meador-Woodruff, 2004), while protein expression studies in this area have found increased GluN2B (Clinton *et al.*, 2006). More recently, a comprehensive study of ionotropic glutamate receptor transcript expression in thalamic nuclei found no differences in GluN1 or GluN2 isoforms in schizophrenia (Dracheva *et al.*, 2008). In the striatum, no abnormal ionotropic glutamate receptor transcript expression has been found (Meador-Woodruff *et al.*, 2001b) but in the substantia nigra pars compacta, GluN1 was reported to be increased in schizophrenia (Mueller *et al.*, 2004).

AMPA receptors

Examination of the expression of AMPA receptors in postmortem brain in schizophrenia has yielded subunit-specific findings that also appear to be region specific (Table 3). As with NMDA receptors, variable and often contradictory data have been reported. In the prefrontal cortex of schizophrenia patients, a recent study found decreased GluA1 and GluA2 protein expression (Corti *et al.*, 2011), while binding studies did not find changes in AMPA receptor expression in this area (Healy *et al.*, 1998). At the transcript level, no changes

in AMPA subunits were found (Healy *et al.*, 1998). A recent report focusing on AMPA receptor trafficking in the DLPFC found an increase in GluA1 subunit protein expression in an early endosome compartment, suggesting trafficking abnormalities in this area (Hammond *et al.*, 2010). Discrepancies have been found in mRNA studies in DLPFC in schizophrenia. While some studies report decreased GluA2 and GluA4 transcripts (Beneyto and Meador-Woodruff, 2006), others found an increase in GluA2 and GluA4 in this same area (Dracheva *et al.*, 2005). In the occipital cortex, one study found increased GluA4 transcript levels (Dracheva *et al.*, 2005).

In the hippocampus, decreased AMPA receptor binding in CA4/CA3 and CA2 regions have been reported in schizophrenia (Kerwin *et al.*, 1990; Eastwood *et al.*, 1997b; Gao *et al.*, 2000), together with decreased expression of GluA1 and GluA2 AMPA receptor transcripts (Harrison *et al.*, 1991; Eastwood *et al.*, 1995; Eastwood *et al.*, 1997a). Another study, however, failed to show AMPA receptor binding changes in this area (Beneyto *et al.*, 2007).

While some studies found no change in mRNA expression in the thalamus in schizophrenia (Dracheva *et al.*, 2008), others report abnormal GluA1 and GluA3 subunit transcript expression (Ibrahim *et al.*, 2000). In the striatum, no changes in AMPA receptor have been reported in this illness (Meador-Woodruff *et al.*, 2001b; Noga and Wang, 2002). In the caudate, however, two binding studies found opposite outcomes, where one found an increase in binding (Noga *et al.*, 1997), and another found a decrease in binding in this area and in the nucleus accumbens (Noga and Wang, 2002).

Kainate receptors

Kainate receptor expression changes in schizophrenia are relatively less consistent than those seen for NMDA receptors (Table 3). In the prefrontal cortex, binding studies have found an increase, decrease or no change in kainate receptors (Nishikawa *et al.*, 1983; Meador-Woodruff *et al.*, 2001a; Zavitsanou *et al.*, 2002; Scarr *et al.*, 2005), while transcript studies report decreased GluK2 and GluK3 mRNA in this area (Sokolov, 1998). In the DLPFC, conflicting transcript data has been reported, finding decreased or no change in GluK1 and decreased GluK5 levels (Meador-Woodruff *et al.*, 2001a; Scarr *et al.*, 2005). Transcript analysis also suggested altered GluK1 expression in the perirhinal cortex in schizophrenia (Beneyto *et al.*, 2007; Woo *et al.*, 2007), but several studies have failed to find any changes in protein expression of kainate receptor subunits in this area or in the ACC (Breese *et al.*, 1995; Zavitsanou *et al.*, 2002). A study measuring co-expression of GluK1 and GAD67 transcripts in the ACC in schizophrenia reported a decrease in GluK1 in GAD67 containing neurons (Beneyto *et al.*, 2007). In the orbitofrontal cortex, a decrease in the number of cells expressing kainate receptors has been reported in this illness (Garey *et al.*, 2006).

In the hippocampus, conflicting data have been reported. Binding studies report decreased or no change in kainate receptors (Kerwin *et al.*, 1990; Gao *et al.*, 2000); while decreased transcript expression of GluK2 and GluK5 subunits was found (Porter *et al.*, 1997). At the protein level, a study in apical dendrites reported decreased dendritic expression of GluK1, K2 and K3 subunits in the CA1, CA2 and CA3 areas of the hippocampus (Benes *et al.*, 2001), but another study in crude hippocampal extracts found no changes in the same kainate subunits in this area (Breese *et al.*, 1995).

In the thalamus, a decrease in neuronal GluK2 and GluK3 and a decrease in GluK5 transcript have been reported (Ibrahim *et al.*, 2000; Sodhi *et al.*, 2011). No changes in kainate receptors were found in the striatum (Meador-Woodruff *et al.*, 2001b).

Metabotropic glutamate receptors

There has been recent interest in the role of the metabotropic glutamate receptors in schizophrenia, especially focusing in the group II family (Table 3). Because of the lack of specific antibodies against mGluR2 and mGluR3, there have been conflicting reports on the expression of these receptors. Most recently, using specific antibodies targeted to mGluR3, the monomeric form of this receptor was shown to be decreased in prefrontal cortex in schizophrenia (Ghose *et al.*, 2009). Another study with specific antibodies found no change of mGluR3 monomers in prefrontal cortex but a decrease in mGluR3 dimers (Corti *et al.*, 2007). Most studies done at the transcript level have found no change in mGluR3 mRNA (Ohnuma *et al.*, 1998; Richardson-Burns *et al.*, 2000; Gupta *et al.*, 2005; Ghose *et al.*, 2008). Unlike mGluR3, mGluR2 protein expression appears to remain unchanged in the prefrontal cortex in schizophrenia (Crook *et al.*, 2002; Ghose *et al.*, 2008), while transcript level studies have produced conflicting results, showing an increase in the white matter of the prefrontal cortex or a decrease in mGluR2 expression in this same area (Ghose *et al.*, 2008; Gonzalez-Maeso *et al.*, 2008).

Group I metabotropic receptors modulate NMDA receptors and have been studied as possible candidates disrupted in schizophrenia. Genetic linkage studies suggest that mGluR5 is involved in schizophrenia, and increased mGluR5 and mGluR1 transcript, and mGluR1 protein expression have been found in prefrontal cortex in this illness (Ohnuma *et al.*, 1998; Devon *et al.*, 2001; Gupta *et al.*, 2005; Volk *et al.*, 2010), further supporting a possible role of group I metabotropic receptors in the pathophysiology of schizophrenia.

Group III metabotropic receptors have been less studied. Human polymorphism studies failed to find an association between mGluR4 and schizophrenia (Ohtsuki *et al.*, 2001; Shibata *et al.*, 2009), while more promising results were found for mGluR8 and mGluR7 in single nucleotide polymorphism screenings, where at least one susceptibility locus was described in each gene (Takaki *et al.*, 2004; Shibata *et al.*, 2009).

ASSOCIATED INTRACELLULAR PROTEINS ABNORMALITIES IN SCHIZOPHRENIA

NMDA associated proteins

Proteins that associate specifically with NMDA receptors, such as PSD95, PSD93, SAP102, and NF-L modulate NMDA receptor function by promoting clustering and anchoring at the synaptic membrane and regulating intracellular signaling (Sheng and Pak, 2000). These proteins have been found to be abnormal in multiple brain regions in schizophrenia (Table 4). In the thalamus, the transcript levels of SynGAP, an NMDA receptor interacting protein underlying signaling and trafficking of these receptors, were reported decreased in this area (Sodhi *et al.*, 2011), but PSD95, SAP102, and NF-L transcripts were found to be either elevated or decreased (Clinton *et al.*, 2003; Clinton and Meador-Woodruff, 2004; Clinton *et al.*, 2006). PSD95 protein expression was increased in the thala-

Table 4. Glutamate receptor accessory protein abnormalities in schizophrenia versus comparison subjects

Family	Subunit	Cortex		Hippocampus		Thalamus		B. G.	
		T	P	T	P	T	P	T	P
NMDA accessory proteins	PSD-93	↑[1]	↓[1]			↔[2]		↔[3,4]	
	PSD-95	↑[1,5]/↓[6]/↔[7]	↓[1,8,9]	↔[6]		↑[2]/↓[10]	↑[11]	↔[3,4]	
	SAP102	↔[7]			↓[12]	↑[2]/↓[10]	↔[11]	↓[3,4]	
	NF-L	↓[7]/↑[1]	↓[1]			↑[2]/↓[10]	↔[11]	↔[3,4]	
	SynGAP		↓[8]			↓[13]			
	APBA1	↑[14]	↔[14]						
	mLin2/CASK	↑[14]	↓[14]						
	mLin7A/Veli-1	↑[14]	↔[14]						
	mLin7C/Veli-3	↑[14]	↓[14]						
	Kif17	↔[14]	↔[14]						
	Yotiao							↔[4]	
AMPA accessory proteins	GRIP1	↑[15]	↑[16]/↔[12]			↓[13]			
	TARP2	↑[17]							
	PICK1	↓[17]							
	SAP97	↓[12]	↓[12]/↑[16]						
	NSF	↓[18,19]/↔[17]	↔[17]						
	Syntenin	↔[17]							

T: Transcript, P: Protein, B. G.: Basal ganglia, ↑: increased, ↓: decreased, ↔: unchanged. [1]Kristiansen *et al*., 2006; [2]Clinton *et al*., 2003; [3]Kristiansen *et al*., 2010a; [4]Mueller *et al*., 2004; [5]Dracheva *et al*., 2001; [6]Ohnuma *et al*., 2000; [7]Beneyto and Meador-Woodruff, 2008; [8]Funk *et al*., 2009; [9]Kristiansen *et al*., 2010b; [10]Clinton and Meador-Woodruff, 2004; [11]Clinton *et al*., 2006; [12]Toyooka *et al*., 2002; [13]Sodhi *et al*., 2011; [14]Kristiansen *et al*., 2010a; [15]Dracheva *et al*., 2005; [16]Hammond *et al*., 2010; [17]Beneyto and Meador-Woodruff, 2006; [18]Mirnics *et al*., 2000; [19]Whiteheart and Matveeva, 2004.

mus, while in the prefrontal cortex no changes were seen in SAP102 protein expression (Toyooka *et al*., 2002; Clinton *et al*., 2003). At the transcript level, PSD95 was found decreased, increased or exhibiting no change in the cortex, while the protein level was decreased (Ohnuma *et al*., 1998; Kristiansen *et al*., 2006; Beneyto and Meador-Woodruff, 2008; Funk *et al*., 2009; Kristiansen *et al*., 2010b). NF-L transcript expression was shown either decreased or increased in DLPFC (Beneyto and Meador-Woodruff, 2008), while it's protein expression was reported to be decreased in this area (Kristiansen *et al*., 2006). SAP97, which is associated with AMPA GluA1 subunits but also targets NMDA and kainate receptors to dendritic spines, was found to be decreased in the prefrontal cortex in schizophrenia (Toyooka *et al*., 2002; Li *et al*., 2011). In the ACC, the protein expression of SynGAP was found decreased (Funk *et al*., 2009). Several microtubule-associated trafficking complex proteins, including KIF17, APBA1, CASK, and mLin7 were also found to be abnormally expressed at the transcript and protein level in the cortex in schizophrenia, suggesting abnormal NMDA receptor trafficking in this illness (Kristiansen *et al*., 2010a). In the hippocampus, only SAP102 protein has been found to be decreased (Toyooka *et al*., 2002).

AMPA associated proteins

Recent investigations have moved beyond studies of glutamate receptors to include direct measurement of glutamate receptor auxiliary molecules that regulate receptor function and localization (Table 4). Significant and region-specific changes in these molecules have been reported in schizophrenia. In the DLPFC, decreased transcript expression of PICK1, a protein that interacts with GluA2-4 containing AMPA receptors, was found (Dev *et al*., 1999; Lu and Ziff, 2005; Beneyto and Meador-Woodruff, 2006). Decreased transcript expression of SAP97, a GluA1-interacting protein, was reported in the DLPFC, while protein studies of this molecule in this area yielded conflicting results, being increased in one study, but decreased in another (Toyooka *et al*., 2002; Hammond *et al*., 2010). TARP2 transcript was also reported to be increased in the DLPFC in schizophrenia, suggesting abnormal intracellular receptor localization in this illness (Beneyto and Meador-Woodruff, 2006). The transcript expression of NSF, a GluA2 interacting protein, and SAP97, a GluA1 associated protein, were found to be decreased in the prefrontal cortex (Mirnics *et al*., 2000; Toyooka *et al*., 2002; Whiteheart and Matveeva, 2004), while SAP97 protein expression was found to be either increased or decreased in this area (Hammond *et al*., 2010). GRIP, which interacts with the GluA2 subunit, is increased at both the transcript and protein level in the cortex (Dracheva *et al*., 2005; Hammond *et al*., 2010). mRNA levels of GRIP and ABP, another receptor interacting protein, were also increased in the occipital cortex (Dracheva *et al*., 2005). In the thalamus, a decrease in transcript expression of GRIP1 has been reported (Sodhi *et al*., 2011).

ANTIPSYCHOTIC DRUGS TARGETING GLUTAMATERGIC RECEPTORS

Given that multiple studies in the brain in schizophrenia have revealed abnormalities in the molecules associated with glutamate neurotransmission in this illness, new drug development targeting the glutamate synapse has become an area

of great interest. Glutamatergic neurotransmission involves many molecules, including pre- and post-synaptic receptors, intracellular receptor-interacting proteins that link glutamate receptors to signal transduction pathways, and membrane- and vesicle-bound glutamate transporters. All of these molecules are potential targets for drug development. Recent efforts have focused on modulation of the glutamate receptors, especially the NMDA subtype, as reviewed below. Given the complexity of the glutamate synapse, however, there is great potential for further new drug development that could profitably target other molecules associated with glutamate neurotransmission for use in treating this psychiatric illness.

NMDA receptor co-agonist site modulators

Because NMDA receptor hypofunction has been implicated in schizophrenia, treatment of this illness by modulating this system by the administration of glutamate or a related agonist would superficially seem to be an obvious starting point. However, excessive activation of glutamate receptors can lead to neurotoxicity. Toxicity and pharmacodynamic/kinetic issues have led to the development of alternative pharmacological approaches to modulate NMDA and other glutamate receptors.

D-Serine is a selective, full agonist at the glycine co-agonist site on NMDA receptors, and as such it increases the activation of the receptor in the presence of endogenous glutamate. Patients with schizophrenia showed an improvement in positive, negative and cognitive symptoms when 30 mg/kg/day of D-serine was added as an adjuvant to non-clozapine antipsychotic regimes (Tsai *et al.*, 1998; Heresco-Levy *et al.*, 2005). In contrast, another trial showed no differences between placebo and D-serine adjuvant therapy (Lane *et al.*, 2010). A recent meta-analysis taking into consideration the number of trials and sample size in subgroup analyses, concluded than when added to non-clozapine antipsychotic treatment, D-Serine is therapeutically beneficial, resulting in improvement of negative and total schizophrenia symptoms (Singh and Singh, 2011).

Glycine, another full agonist of the NMDA co-agonist site, has been tested by itself and as also an adjuvant for treatment of schizophrenia. The most compelling evidence of the benefits of glycine adjuvant treatment in schizophrenia comes from a series of glycine augmentation studies done by Javitt *et al.* (Javitt *et al.*, 1994; Javitt, 1996; Javitt *et al.*, 2001; Javitt, 2002). Increasing doses of glycine from 30 g/day to 60 g/day have found improvement of both negative and cognitive symptoms (Javitt *et al.*, 1994; Javitt, 1996; Javitt *et al.*, 2001; Javitt, 2002). Similarly, a meta-analysis showed that glycine improved positive and total symptom scores when used as an adjuvant to non-clozapine antipsychotics, but worsened these symptoms when added to clozapine (Singh and Singh, 2011). Overall, glycine appears to be effective in the treatment of schizophrenia when given as an adjuvant to non-clozapine antipsychotic treatment.

D-cycloserine is an NMDA glycine binding site partial agonist that when added to non-clozapine antipsychotic drugs can be effective for treating the negative symptoms of schizophrenia but within a narrow therapeutic window (Goff *et al.*, 1999a; Evins *et al.*, 2002; Heresco-Levy and Javitt, 2004; Goff *et al.*, 2005). Optimal doses of D-cycloserine were established at 50 mg/kg, with larger doses of 250 mg/kg resulting in worsening of positive symptoms (Buchanan *et al.*, 2007). Interestingly, worsening of negative symptoms was seen when D-cycloserine was added to atypical antipsychotics such as clozapine (Goff *et al.*, 1996; Goff *et al.*, 1999b). More recently, a trial comparing chronic administration of D-cycloserine in addition to conventional antipsychotics found no improvement (Goff *et al.*, 2005). Because of the conflicting outcomes of these studies, the efficacy of D-cycloserine in the treatment of schizophrenia remains controversial.

One study has investigated the effect of D-alanine, an endogenous full agonist of the co-agonist site of the NMDA receptor, in schizophrenia (Tsai *et al.*, 2006). This study was a double blind placebo-controlled trial of 100 mg/kg/day of D-alanine added to antipsychotic treatment. This resulted in significant improvement in positive, negative and cognitive symptoms, making D-alanine another promising adjuvant for schizophrenia treatment.

Sarcosine, a glycine transporter-1 inhibitor, activates the NMDA receptor co-agonist site by increasing the concentration of glycine in the synaptic cleft (Bergeron *et al.*, 1998; Javitt, 2006). Similar to other glycine modulators, sarcosine had no effect when added to clozapine (Lane *et al.*, 2006). However, when 2 g/day were added to conventional antipsychotic drugs or risperidone, there was a significant improvement of positive, negative, and depressive symptoms and general psychopathology scores in schizophrenia (Tsai *et al.*, 2004). A recent meta-analysis has shown that sarcosine improves negative and total symptom scores in schizophrenia (Singh and Singh, 2011). Sarcosine was also beneficial for acute exacerbation of schizophrenia symptoms, improving the response to standard medication (Lane *et al.*, 2008) and possibly being more beneficial than D-serine adjuvant therapy in this phase of the illness (Lane *et al.*, 2005).

Milacemide is a prodrug of glycine which readily crosses the blood brain barrier and was studied as a possible NMDA receptor agonist. Studies in schizophrenia have not yielded promising results, since low doses of this compound have no effect in schizophrenia symptoms while high doses exacerbate negative symptoms (Rosse *et al.*, 1990; Rosse *et al.*, 1991).

In summary, NMDA receptor glycine co-agonist site modulators are promising targets for adjuvants of an ongoing conventional antipsychotic drug treatment. Their use with atypical antipsychotics, however, may result in worsening of symptoms in schizophrenia, which may be due to unique effects of atypical antipsychotics on NMDA receptors.

AMPA receptor potentiators

Given the importance of AMPA receptors for fast excitatory neurotransmission and alterations of AMPA receptor subunits and associated proteins in schizophrenia, targeting these receptors may have potential therapeutic roles in the treatment of this illness. Ampakines are a novel class of compounds that function by decreasing desensitization and deactivation rates of the AMPA channel, effectively increasing the opening time of the channel and the receptor response to glutamate (Arai *et al.*, 1996). There are several families of AMPA receptor potentiators: pyrrolidinones, which include piracetam and aniracetam; the ampakines 1-BCP, Org 26576, Org 24448, CX516 and CX546; benzothiadiazides, such as cyclothiazide; and the biarylpropylsulfonamide, LY404187 (Jordan *et al.*, 2005). Preclinical studies have shown these drugs can facilitate LTP, learning and memory, hippocampal neurogenesis and neurotrophic factor expression. They also act in an antidepressant-

like manner and affect serotonin neurotransmission (Jordan *et al.*, 2005; Goff *et al.*, 2008).

Piracetam was the first ampakine to be studied in schizophrenia, and was found to improve positive symptoms when combined with haloperidol during an 8-week trial (Noorbala *et al.*, 1999). A preliminary trial performed by Goff *et al.* (Goff *et al.*, 2001) evaluated the effect of CX516 on 19 schizophrenia patients being simultaneously treated with clozapine, and found improvements in executive brain functions such as memory and attention. However, a follow-up study by the same group found no change in cognition or other schizophrenia symptoms when patients were treated with CX516 and either clozapine, olanzapine, or risperidone for 4 weeks (Goff *et al.*, 2008). Although ampakines may theoretically be a promising therapeutic approach, there is currently no clear clinical evidence of their effectiveness in treating the symptoms of schizophrenia.

mGluR modulators

Given the modulatory action of mGluRs on NMDA receptors, a number of positive allosteric modulators targeted to type II mGluRs are currently in development (Imre, 2007). Because the binding sites for ligands across members of the mGluR subtypes are often highly conserved, it is difficult to achieve subtype specific selectivity. A glutamate analog that selectively binds to mGluR2/3, LY-404039, has displayed promising antipsychotic effects improving positive and negative symptoms in schizophrenia (Chaki, 2010; Chaki and Hikichi, 2011). Studies in a rodent model have shown that LY-404039 acts through the activation of mGluR2 rather than mGluR3, suggesting an association of mGluR2 with antipsychotic-like properties. This, however, has not yet been evaluated clinically (Fell *et al.*, 2008). Further suggesting a promising role for mGluR2 modulators in the treatment of psychotic symptoms, a selective potentiator of mGluR2, LY-487379, has shown promising results in rodents models (Galici *et al.*, 2005). More recently, several highly selective allosteric modulators of mGluR5 have been developed (Kanuma *et al.*, 2010), and together with other mGluR activators are targets of studies for the treatment of psychiatric and neurological disorders.

Kainate receptor antagonists

While NMDA and AMPA receptors have been the targets for most drug discovery around glutamate receptors, relatively little has been done to target the kainate receptor. The AMPA/kainate receptor antagonist LY293558 has been shown to ameliorate psychotic-like symptoms induced by ketamine (Moghaddam *et al.*, 1997), but no clinical trials have been done with this compound or any other selective kainate receptor antagonist. Topiramate, a drug with partial activity, is a kainate receptor antagonist, reduces mood symptoms but does not have additional effects on positive or negative symptoms in schizophrenia when administered with other antipsychotics (Tiihonen *et al.*, 2005).

Other glutamatergic drugs

Memantine is an NMDA receptor antagonist, used for the treatment of Alzheimer's disease. It acts as a non-competitive, low-affinity, voltage-dependent NMDA receptor antagonist that binds to the magnesium blocking site with higher affinity than magnesium, thus inhibiting the influx of calcium ions (Kornhuber *et al.*, 1989). Several studies have found that memantine given together with clozapine improves positive and negative symptoms in refractory schizophrenia patients (Gama *et al.*, 2005; Krivoy *et al.*, 2008; de Lucena *et al.*, 2009). Another large study, however, did not find an improvement in schizophrenia symptoms with adjuvant memantine treatment but rather found an increase in adverse effects (Lieberman *et al.*, 2009). Although the effects of memantine on positive and negative symptoms of schizophrenia have conflicting results, memantine has proven useful for the treatment of catatonia (Thomas *et al.*, 2005; Carpenter *et al.*, 2006; Carroll *et al.*, 2006).

First used to treat alcoholic patients in Europe, acamprosate is currently being considered for the treatment of schizophrenia due to its modulatory action on synaptic glutamate release and NMDA receptor function (Naassila *et al.*, 1998; De Witte *et al.*, 2005; Paz *et al.*, 2008). Interestingly, acamprosate may act through mGluR5 without abolishing normal synaptic transmission. Acamprosate can also bind to the polyamine modulator site of the NMDA receptor and may be able to act as either an agonist or antagonist at the NMDA receptor (Paz *et al.*, 2008). Studies have yet to be reported examining the effectiveness of this drug on treating schizophrenia-like symptoms; however, in patients with schizophrenia and alcohol dependence, Ralevski *et al.* found that treatment with acamprosate did not negatively affect cognitive outcome or levels of alcohol consumption in these patients (Tek *et al.*, 2008; Ralevski *et al.*, 2011).

SUMMARY

Abnormalities of dopaminergic neurotransmission have long been held to be critical to understanding the pathophysiology of schizophrenia, and most treatments have targeted dopamine receptors. Recent advances have pointed to abnormalities of other neurotransmitters being involved in schizophrenia, especially dysregulation of glutamate transmission in this illness. Numerous studies have now been reported that have measured molecules associated with glutamate neurotransmission in the brain in schizophrenia, and abnormalities of multiple receptors and receptor-associated proteins have now been identified. Glutamatergic neurotransmission involves myriad molecules, including pre- and post-synaptic receptors, intracellular receptor-interacting proteins that link glutamate receptors to signal transduction pathways, and membrane- and vesicle-bound glutamate transporters which remove glutamate from the synaptic cleft and then package it into vesicles for release. Of the large number of molecules associated with glutamatergic neurotransmission, the strongest evidence for abnormalities of this transmitter system in schizophrenia involves disturbances of the glutamate receptors, specifically the NMDA and AMPA subtypes. Recent efforts at new treatment development have focused on modulation of the NMDA and AMPA receptors, and more recently the metabotropic glutamate receptors have been targeted as well. Early results, especially strategies that target the glycine-binding co-agonist site of the NMDA receptor, have been promising thus far. Given the complexity of the glutamate synapse, many other molecules are potential targets for new drug discovery in attempts to develop more effective treatments for this illness.

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