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Review

Glutamate signaling in the pathophysiology and therapy of schizophrenia

Chieh-Hsin Lin [a,b], Hsien-Yuan Lane [b,c], Guochuan E. Tsai [d,*]

[a] Department of Psychiatry, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[b] Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
[c] Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan
[d] Department of Psychiatry, Harbor-UCLA Medical Center HH212, 1000 W. Carson Street, Torrance, CA 90509, USA

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ABSTRACT

Glutamatergic neurotransmission, particularly through the N-methyl-D-aspartate (NMDA) receptor, has drawn attention for its role in the pathophysiology of schizophrenia. This paper reviews the neurodevelopmental origin and genetic susceptibility of schizophrenia relevant to NMDA neurotransmission, and discusses the relationship between NMDA hypofunction and different domains of symptom in schizophrenia as well as putative treatment modality for the disorder. A series of clinical trials and a meta-analysis which compared currently available NMDA-enhancing agents suggests that glycine, D-serine, and sarcosine are more efficacious than D-cycloserine in improving the overall psychopathology of schizophrenia without side effect or safety concern. In addition, enhancing glutamatergic neurotransmission via activating the AMPA receptor, metabotropic glutamate receptor or inhibition of D-amino acid oxidase (DAO) is also reviewed. More studies are needed to determine the NMDA vulnerability in schizophrenia and to confirm the long-term efficacy, functional outcome, and safety of these NMDA-enhancing agents in schizophrenic patients, particularly those with refractory negative and cognitive symptoms, or serious adverse effects while taking the existing antipsychotic agents.

Contents

1. Introduction

There are plenty of studies which have suggested that dysregulation of dopaminergic (Davis et al., 1991; Toda and Abi-Dargham, 2007), γ-aminobutyric acid (GABA) (Benes and Berretta, 2001; Lewis et al., 2005), glutamatergic (Goff and Coyle, 2001; Moghaddam, 2003)

* Corresponding author. Tel.: +1 310 781 1401; fax: +1 310 781 1093.
E-mail address: etsai@labiomed.org (G.E. Tsai).

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neurotransmission and their interactions (Carlsson et al., 2001) are involved in the pathophysiology of schizophrenia. Among these, the hypofunction of N-methyl-D-aspartate (NMDA) glutamatergic neurotransmission has gained much attention since two decades ago (Olney and Farber, 1995; Javitt, 2008).

Conventional antipsychotics, which block D2 dopamine receptors (Farde et al., 1986), exert effects mainly on positive symptoms. Second-generation antipsychotics (SGAs) have been suggested to be superior to conventional agents in terms of efficacy for positive symptoms, negative symptoms and cognitive deficits but the therapeutic gain is modest (Green et al., 1997; Lane and Chang, 1999; Leucht et al., 2003; Livingston, 1994). Overall, there is a considerable percentage of patients resistant or only partially responsive to available antipsychotic medications (Lieberman et al., 2005). Life threatening side-effect profiles of SGAs, particularly the metabolic syndrome, limit the clinical use of these agents (Lu et al., 2004; Newcomer, 2007; Simon et al., 2009). Moreover, most schizophrenic patients still suffer from lifelong illness and deteriorating function (Hwu et al., 2002; Malla and Payne, 2005; Tsuang et al., 2000). Hence, there is a great need to develop new therapies that will provide better long-term efficacy, functional improvement and safety profiles for schizophrenic patients.

1.1. Glutamate receptors: ionotropic and metabotropic receptors

Glutamate is the most abundant amino acid neurotransmitter in the mammalian brain. There are two types of glutamate receptors: metabotropic and ionotropic receptors. More evidence regarding the involvement of glutamatergic system in schizophrenia focuses on the ionotropic receptors which are subdivided to 3 subtypes: NMDA, quisqualate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (Lodge, 2009). Relief of the depolarization blockade of NMDA receptor requires the activation of non-NMDA receptor. Studies on long-term potentiation (LTP) indicate that NMDA receptors interact with AMPA receptors (Yu et al., 2008). However, the NMDA receptor is the best studied and most relevant subtype of glutamate receptors to understand the pathophysiology of schizophrenia. The NMDA receptor has been demonstrated to play an important role in neurocognition and neurotoxicity (Lipson and Rosenberg, 1994; Kalia et al., 2008). The psychosis due to the blockade of the NMDA receptor is similar to the clinical manifestation of schizophrenia. Up to date, NMDA synapse remains to be the only therapeutic target that is confirmed to have clinical efficacy. Thus, we will focus on the glutamatergic neurotransmission via NMDA receptor in the following review.

1.2. NMDA receptor and synapse

In addition to the agonists and coagonists, the NMDA receptor can be regulated by a variety of molecules, including polyamines, proton, zinc, magnesium, phencyclidine (PCP) and ketamine. These sophisticated regulatory mechanisms suggest that NMDA receptor can adapt to endogenous and exogenous signals to maintain and facilitate a variety of vital brain functions including cognition, memory, neurodevelopment, synaptic plasticity and psychosis (Bliss and Collingridge, 1993).

The NMDA receptor is composed of multiple subunits including NR1 and one of either the NR2 (NR2 A–D) or NR3 (NR3 A–B) to form heteromeric receptor-channels with different pharmacologic and biophysical characteristics (Laurie and Seeburg, 1994) (Fig. 1). The NMDA receptor possesses a number of unique characteristics. For example, it has binding sites not only for glutamate or aspartate, but also a separate coagonist site for the endogenous ligands, D-serine, D-alanine, and glycine. Occupancy of the coagonist site can increase the frequency of opening of the channels activated by NMDA agonists, facilitating excitatory transmission in the brain (Johnson and Ascher, 1987). In fact, the binding of both glycine (or D-serine, D-alanine (Chessell et al., 1991)) and glutamate is required to open the NMDAR channel ionophore (Mayer et al., 1989; Nong et al., 2003; Thomson et al., 1989) (Fig. 1).

Since D-alanine, which presents only in the pituitary, is less likely to play physiological role in the neocortex, most studies focused on the binding of D-serine and glycine on the D-serine/glycine site of NMDAR. Endogenous D-serine/glycine site agonists also play a role in neuromodulation. Binding to the D-serine/glycine site enhances the affinity and efficacy of the glutamate neurotransmission (Fadda et al., 1988), increases the duration and frequency of the open channel state (Vyklický et al., 1990), and promotes turnover of the NMDAR (Nong et al., 2003). Distribution of D-serine parallels to that of NR1, and D-Serine binds more tightly to the NMDAR than glycine (Furukawa and Gouaux, 2003).

The NMDAR D-serine/glycine site on the NR1 subunit is not fully saturated at synapses in brain regions such as the prefrontal cortex, neocortex, hippocampus, thalamus and brainstem slices, suggesting that agonists of the D-serine/glycine site are capable of regulating NMDAR-mediated neurotransmission (Labrie and Roder, 2010). Glycine is abundant throughout the brain and serves as a major inhibitory neurotransmitter in the hindbrain. Synaptic concentrations of glycine are primarily derived from astroglial cells, and its clearance is mediated by glycine transporter 1 (GlyT-1) (Kinney et al., 2003; Lim et al., 2004). D-Serine has been found to be more potent than glycine in targeting the D-serine/glycine site of most NMDARs (Boehning and Snyder, 2003).

Treatment with DAO results in depletion of D-serine which has been shown to attenuate NMDAR activity in cerebellar and hippocampal slices, hippocampal cell cultures, and retina preparations (Mothet et al., 2000; Gustafson et al., 2007). Supporting the physiological role, DAO inhibitor can facilitate the effects of D-serine on prepulse inhibition (PPI) (Hashimoto et al., 2009). D-Serine levels were reduced in the cerebrospinal fluid of drug na ve patients with schizophrenia (Hashimoto et al., 2005; Bendikov et al., 2007). Diminished D-serine along with elevation in L-serine also suggests a dysfunction of serine racemase (SRR) activity (Hashimoto et al., 2003). Changes in SRR protein expression have been found in the postmortem brains of schizophrenic individuals (Bendikov et al., 2007; Steffek et al., 2006; Verrall et al., 2007). Similarly, glycine levels have been found to be reduced in drug-free schizophrenic individuals and inversely correlate with the severity of negative symptoms (Sumiyoshi et al., 2004; Neeman et al., 2005). However, high-dose glycine impairs the prepulse inhibition measure of sensorimotor gating in humans, which does not support the glycine treatment for cognition (O'Neill et al., 2010). Due to glycine's complex metabolism of both excitatory and inhibitory signaling, D-serine is likely a better choice than glycine when considering applying full agonist for treatment.

Other regulators involved in the metabolism of D-serine such as D-amino acid oxidase (DAO) (Verrall et al., 2007; Bendikov et al., 2007), protein-interacting with kinase C (PICK1) (Beneyto and Meador-Woodruff, 2006) and alanine–serine–cysteine transporter 1 (Asc-1) (Burnet et al., 2008) were also found to be related to the D-serine levels. Depletion of D-serine was found to be associated with NMDAR-mediated neurological functions and NMDAR-induced neurotoxicity, as well as NMDAR-dependent LTP in many brain regions especially the hippocampus (Gustafson et al., 2007; Shleper et al., 2005; Mothet et al., 2006). D-Serine supplement can entirely reverse the effects of decreased NMDAR-mediated neurotransmission (Mothet et al., 2000, 2006; Yang et al., 2003; Panatier et al., 2006; Gustafson et al., 2007), moreover, enhance NMDAR signaling demonstrated both in vitro (Chen et al., 2003; Martina et al., 2003; Yang et al., 2003; Chapman et al., 2003) and in mice which lack DAO activity (Wake et al., 2001), Acs-1 (Xie et al., 2005) or have diminished GAD67 expression (Reynolds et al., 2004; Torrey et al., 2005). In human genetic studies, significant associations between DAO (Ohnuma et al., 2009) and G72 (DAOA)/G30 (Shinkai et al., 2007) gene polymorphisms and schizophrenia were also observed in case–control association analyses.