



Early Identification and Intervention of Schizophrenia: Insight From Hypotheses of Glutamate Dysfunction and Oxidative Stress

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Schizophrenia is a severe mental disorder which leads to functional deterioration. Early detection and intervention are vital for better prognosis. However, the diagnosis of schizophrenia still depends on clinical observation to date. Without reliable biomarkers, schizophrenia is difficult to detect in its early phase. Further, there is no approved medication for prodromal schizophrenia because current antipsychotics fail to show satisfactory efficacy and safety. Therefore, to develop an effective early diagnostic and therapeutic approach for schizophrenia, especially in its prodromal phase, is crucial. Glutamate signaling dysfunction and dysregulation of oxidative stress have been considered to play important roles in schizophrenic prodrome. The N-methyl-D-aspartate receptor (NMDAR) is one of three types of ionotropic glutamate receptors. In this article, we reviewed literature regarding NMDAR hypofunction, oxidative stress, and the linkage between both in prodromal schizophrenia. The efficacy of NMDAR enhancers such as D-amino acid oxidase inhibitor was addressed. Finally, we highlighted potential biomarkers related to NMDAR and oxidative stress regulation, and therefore suggested the strategies of early detection and intervention of prodromal schizophrenia. Future larger-scale studies combining biomarkers and novel drug development for early psychosis are warranted.

Keywords: glutamate, N-methyl-D-aspartate receptor, oxidative stress, early psychosis, schizophrenia, prodrome, biomarker

INTRODUCTION

Schizophrenia is a high-morbidity and high-mortality brain disorder. Globally 1% population suffered from this disorder. The common symptoms of schizophrenic patients include hallucination, delusion, disorganized thought and behavior, and negative symptoms. Clinical manifestation of schizophrenia consists of three domains: positive symptoms (such as hallucinations or delusions), negative symptoms (such as flattening affect or social withdrawal), and cognitive deficits (such as impaired memory, attention, and executive functions) (1–4). Among them, cognitive function impairments are considered to be core symptoms of schizophrenia, starting from its prodromal phase, while psychotic symptoms have not yet been vivid

(5–9). Cognitive deterioration appears at an earlier age in schizophrenia patients (10, 11). The deterioration of cognitive function in patients with schizophrenia will lead to impairment of self-care, social, and occupational function (12). Therefore, the social impact of schizophrenia is very high. Current antipsychotics have limited, if any, efficacy for cognitive function.

The etiology of schizophrenia remains unclear. Oxidative stress and glutamate-related dysfunction, potentiating each other in a vicious circle, are interdependently involved in the pathogenesis of schizophrenia (13, 14). Adolescence or early adulthood is the critical period when schizophrenia typically arises, while glutamate is the main excitatory neurotransmitter that mediates puberty (15). Oxidative stress and genetic/environmental factors converge during neurodevelopment, leading to the impairment of neural connectivity and synchronization, as well as to cognitive deficits in early psychosis patients (16).

This review highlights a recent development surrounding N-methyl-D-aspartate receptor (NMDAR) modulators and antioxidants, paving the way for biomarker guided early detection and intervention of high-risk individuals (17).

IMPORTANCE OF EARLY DETECTION AND INTERVENTION OF SCHIZOPHRENIA

Most individuals experience a period of prodromal symptoms prior to the diagnosis of schizophrenia (18). Before full-blown psychotic symptoms appear, individuals may experience changes in cognition, behavior, and function (19). Therefore, it is crucial to identify populations at high risk of schizophrenia to initiate early intervention (20). Improved diagnostic tools, the advent of atypical antipsychotic and the development of phase-specific psychosocial treatments have made intervention research in people at prodrome or ultra-high risk or people with attenuated psychosis syndrome for developing schizophrenia possible (21).

Antipsychotic medications, however, have not yet been approved for such populations, mainly because prolonged exposure to antipsychotic medication has been associated with various side effects such as weight gain, metabolic syndrome and hyperlipidemia (22, 23). First-generation antipsychotics, which block the majority of D2 dopamine receptors in the putamen (24, 25), mainly exert effects on positive symptoms and generate numerous intolerable side effects such as parkinsonism (including tremor, rigidity, bradykinesia), akathisia, dystonia, and prolactinemia (26). Newer atypical antipsychotics targeting both dopamine D2 and serotonin 5HT₂ receptors (24, 26, 27) have been suggested to be superior to conventional agents in terms of efficacy for positive symptoms and perhaps negative symptoms (28–30). Despite this, there were a considerable percentage of patients resistant or only partially responsive to available medications (31). Moreover, side-effect profiles of second-generation antipsychotics, including obesity, diabetes mellitus, hyperlipidemia, metabolic syndrome, and sudden cardiac death, limit their clinical use (32–34). A substantial portion of schizophrenia patients refuse or cannot tolerate antipsychotics due to poor response and/or side effects (24).

Further, long-term antipsychotics use is associated with cognitive impairment (35).

Most prodromal patients receive no or very brief, if any, antipsychotic treatment, due to safety concerns (36). To date, there is neither approved medication for prodromal schizophrenia, nor reliable outcome predictor for its conversion to full-blown schizophrenia. Therefore, developing early diagnosis and intervention strategy is very important.

THE GLUTAMATE HYPOTHESIS OF SCHIZOPHRENIA

In addition to dopaminergic neurotransmission, glutamatergic neurotransmission has gained more attentions lately as the key deficit of schizophrenia (37–44). Glutamate has two major receptor families: (1) ionotropic receptors, consisting of N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptor subtypes, and (2) metabotropic receptors (mGluRs), which are G-protein-coupled receptors.

While glutamatergic outputs appear widespread over the corticolimbic system, disinhibition of the glutamatergic output from the subiculum to the ventral tegmental area leads to the hyperdopaminergic state with treatment of NMDA receptor (NMDAR) antagonists (45).

HYPOFUNCTION OF NMDAR-MEDIATED NEUROTRANSMISSION IN SCHIZOPHRENIA

NMDAR, a heteromeric ion channel, formed from a number of subunits (NR1, NR2A/NR2B, NR3A, and NR3B), plays an important role in neurocognition. NMDAR antagonists, such as phencyclidine (PCP) and ketamine, induce psychosis which resembles schizophrenia more closely than the amphetamine/dopamine agonist do (46). The former causes not only positive symptoms, but also negative symptoms and cognitive deficits associated with schizophrenia. Moreover, glycine transporter inhibitors could reverse ketamine-induced effects (37, 47–50). Decreases in NMDAR density were found in post-mortem tissue from schizophrenic patients (51). The above evidence suggests that NMDAR dysfunction may be a critical deficit in schizophrenia (40, 43, 44, 52). Modulation of NMDAR has been proposed as a possible therapy for schizophrenia, including its prodrome (26, 37, 48, 53–56).

ABNORMAL PLASTICITY OF AMPA AND KAINATE RECEPTORS IN SCHIZOPHRENIA

While some glutamatergic synapses have only AMPA receptors (AMPA receptors) or only NMDARs, most have both receptors. NMDAR modulators may regulate not only NMDARs but also AMPARs (57). Similar to NMDARs, AMPARs modulate fast glutamate transmission, neuronal circuit remodeling

and higher order cognitive functions such as learning and memory; and abnormalities of AMPAR trafficking contribute to dysfunction in brain diseases such as schizophrenia (58). AMPAR subunits (GluR1-4) assemble to form AMPAR complexes in the lumen of the endoplasmic reticulum. Recently, the possibility of AMPAR dysfunction has been proposed to explain abnormalities in glutamate neurotransmission associated with the pathophysiology of schizophrenia (59). Topiramate, an antiepileptic drug with AMPAR antagonist activity has been demonstrated to improve schizophrenia as an adjunctive therapy; however, its efficacy may occur via GABA neurotransmission, as AMPAR antagonism occurs only at high concentrations (60, 61). Beneficial effects of CX516 and minocycline on cognitive domains appeared insignificant with rigorous statistical analyses (62). Newer AMPAR modulators such as UoS12258 which may possess precognitive properties deserve further studies (63).

Studies of kainate receptors (KARs) met difficulties because of the lack of specific activators or blockers for the receptors. First, kainate can also activate AMPARs. Second, AMPA, activates many KARs too (64).

ROLE OF THE MGLUR ALLOSTERIC MODULATION IN SCHIZOPHRENIA

The mGluRs, consisting of eight subtypes, provide a wide range of targets to modulate NMDAR function as well as glutamate release. Preclinical studies demonstrated that activation of the mGluR2/3 down-regulated the excessive dopamine release caused by treatment with NMDAR antagonists (65). A clinical trial showed that an mGluR2/3 agonist, which down-regulates disinhibited glutamate release, exhibited antipsychotic properties (66). There have also been advances in the discovery of highly selective positive allosteric modulators (PAMs) of mGluR2 and mGluR5 for the treatment of schizophrenia (67). The mGluR5 PAMs counter aberrant neuronal activity generated by NMDAR antagonists in the prefrontal cortex (68). Recently, more subtype-selective allosteric modulators for various mGluRs instill hopes of better or alternative treatments for (subgroups of) schizophrenia (69).

OXIDATIVE STRESS IN SCHIZOPHRENIA

Current evidence supports that increased oxidative stress-induced cellular damage of macromolecules may play a role in schizophrenia, and schizophrenia patients have abnormal antioxidant defenses as observed in their peripheral blood (70–72), CSF (73), and postmortem brain tissues (74, 75). Evidence from genetic studies also suggests that schizophrenia patients may have a reduced ability to mount an adequate antioxidant defense (76).

The failure of antioxidant defenses to protect against free-radical generation damages cell membranes, impacts on neurotransmission and, ultimately, leads to phenotypes of schizophrenia (75). Important free radicals include hydrogen peroxide, the hydroxyl radical, nitric oxide (NO), and the superoxide radical. In the rate-limiting step of purine catabolism,

xanthine oxidase catalyzes the conversion of xanthine to uric acid, an important antioxidant, and generates superoxide radicals. Superoxide dismutase catalyzes the conversion of superoxide radicals to hydrogen peroxide. Both catalase and glutathione peroxidase converts hydrogen peroxide to water and oxygen. Reduced glutathione is oxidized by glutathione peroxidase to oxidized glutathione. Glutathione peroxidase also converts nitrate (a by-product of NO radicals) to nitrite. Nitrite is often used as a marker for NO activity. Hydroxyl radicals, produced from both hydrogen peroxide and NO, promote apoptosis, DNA damage, protein carbonylation, and lipid peroxidation. Vitamin E, also acting as an antioxidant, can inhibit lipid peroxidation. Thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) are important end products of lipid peroxidation (77).

MODULATION OF OXIDATIVE STRESS IN PATIENTS WITH SCHIZOPHRENIA

Clinical trials also support an association between oxidative stress and schizophrenia. Treatment with the antioxidant N-acetylcysteine significantly reduced psychopathology in schizophrenia (78). Nevertheless, N-acetylcysteine may not represent an optimal antioxidant therapy, as its principal modus operandi, the supply of increased cysteine for glutathione biosynthesis, is of limited help unless the brain can use it to produce, recycle and utilize glutathione (13). Another important study also found that supplementation with fish oil significantly reduced the progression to first-episode psychosis in subjects with prodromal symptoms (79). However, many subjects in the study also carried severe depressive symptoms, hampering the conclusion of the study. Anyhow, these findings suggest that oxidative stress levels may be a biomarker of schizophrenia risk and response to adjunctive antioxidant treatment.

LINKING OXIDATIVE STRESS AND NMDAR HYPOFUNCTION IN SCHIZOPHRENIA PATHOGENESIS

Molecular, genetic and pathological evidence suggests that not only oxidative stress but also NMDAR hypofunction contribute to schizophrenia pathophysiology. Evidence now suggests that these factors are mechanistically interdependent and contribute to a common schizophrenia-associated pathology (13, 14).

There are clear similarities between the impact of developmental NMDAR hypofunction and that of oxidative stress on the adult rodent: both cause similar behavioral and cognitive disturbances. Increasing evidence suggests that NMDAR hypofunction and oxidative stress may be reciprocally linked (13, 14, 80). The NMDAR is regulated by redox state: both GRIN1 and GRIN2A possess pairs of reduction-oxidation reaction (redox)-sensitive cysteine residues whose disulfide bond formation decreases NMDAR currents (80), while an overlapping group of cysteine residues are subject to inhibitory S-nitrosylation, which facilitates disulfide bond formation (80, 81).

Recently, it has been shown that changes in intracellular redox status can also modulate NMDAR activity in a manner that is relevant to age-dependent cognitive decline (82). Age-associated shifts in intracellular redox state to a pro-oxidizing environment have been linked to reduced NMDAR activity via the redox regulation of calcium/calmodulin-dependent protein kinase type II (CaMKII), and can be rescued by intracellular glutathione (83).

Whether NMDAR-related dysfunction may influence the modulation of oxidative stress and whether the modulation of oxidative stress can alter NMDAR-related neurotransmission both also deserve further studies.

SEARCHING FOR DIAGNOSTIC AND THERAPEUTIC BIOMARKERS OF SCHIZOPHRENIA

At present, the diagnosis and treatment response of schizophrenia rely on clinical manifestation. There have been lots of post-mortem brain studies (84). However, RNA expressions may be affected by many factors under post-mortem condition. Therefore, it's needed to establish peripheral, accessible biological markers for mental illness (85). Lymphocytes or white cells have been suggested to be a neural probe because numerous studies showed similarities between receptor expression and mechanisms of transduction processes of cells in the nervous system (e.g., neurons and glia) and lymphocytes (86). Blood-derived RNA has become a convenient alternative to traditional tissue biopsy-derived RNA (87).

Several potential markers have been reported. Hashimoto et al reported that serum levels of D-serine were lower in schizophrenic patients than in healthy subjects (88). Besides, the expression of apolipoprotein D was increased in the plasma and brains of individuals with schizophrenia (89). S100B is a calcium-binding protein produced by astroglial cells. It has also been reported that schizophrenic patients, compared with healthy subjects, have higher DRD3 mRNA levels (85) and lower AKT1 protein levels (90) in peripheral lymphocytes. Adrenomedullin mRNA levels in lymphoblastoid cell lines of male schizophrenia patients was higher than in controls (91). Via microarray technique, six genes were suggested to be biomarkers of schizophrenia (92). Another study demonstrated that mRNA expression of eight biomarkers could be discriminated between schizophrenia, bipolar disorder, and controls (87). However, developing more suitable biomarkers for schizophrenia in future studies is warranted because there exists a large overlap between patients and controls in present biomarker studies.

NMDAR- AND OXIDATIVE-RELATED BIOMARKERS OF SCHIZOPHRENIA

NMDAR-related markers are scanty. Lin et al found that the G72 (D-amino acid oxidase activator, DAOA) protein level in plasma was much higher in patients with schizophrenia than in healthy controls (93). G72, functioning as a D-amino acid oxidase (DAAO) activator (DAOA), exists exclusively in 4 primates including humans. The study suggests that peripheral

G72 concentration may be characteristic of schizophrenia. The finding has been replicated independently (94). G72 is a huge protein. Its longest protein is called LG72 and consists of 153 amino acids. Its complex interactions deserve intensive study to elucidate the pathogenesis and pathophysiology of schizophrenia (95). Liquid chromatography-mass spectrometry (LC-MS)-based proteomics and metabolomics that have been used to discover protein and metabolite markers in clinical diseases may be helpful to elucidate the function of G72 and its interaction with other proteins.

A previous study also found that mRNA expression levels of *SLC7A11* and *SLC3A2* were lower in patients with schizophrenia than healthy individuals (96). *SLC3A2* and *SLC7A11* are two subunits of the cystine/glutamate antiporter system x_c^- which plays a critical role in the regulation of glutamate release. DAAO is responsible for degrading D-serine and other D-amino acids (97). A recent study found that its level in peripheral blood was higher with cognitive aging (98). Serine hydroxymethyltransferase 2 (SHMT2) is an isoenzyme that catalyzes the reversible conversion of serine and tetrahydrofolate (THF) to glycine and methylene THF. Phosphoserine aminotransferase 1 (PSAT1) is required for the phosphorylated pathway of L-serine biosynthesis. Uptake of D-serine and L-serine into neurons and astrocytes is predominantly mediated by the serine transporter (ASCT1) subtype. The aforementioned genes/proteins that can regulate glutamate release and NMDAR function may be implicated in the pathogenesis of schizophrenia. Further, a recent study suggests that altered NMDAR signaling and parameters may have the potential to be used to detect vulnerability toward schizophrenia in individuals early in the disease process and thereby enable early intervention in a subgroup of patients (17).

Patients with schizophrenia also exhibit abnormal blood oxidative stress parameters, including total antioxidant status, glutathione peroxidase, catalase, superoxide dismutase, and nitrite (71, 77). It has been suggested that oxidative stress may serve as a potential biomarker in the etiopathophysiology, clinical course (including predicting conversion of high-risk symptoms to psychosis), symptomatology, cognitive function, and treatment response by antioxidants in patients with schizophrenia (16, 77, 99–101).

MISMATCH NEGATIVITY AS AN OBJECTIVE MEASUREMENT FOR NMDA FUNCTION AND A BIOMARKER FOR SCHIZOPHRENIA

Mismatch negativity (MMN) has been proven to be related to NMDAR and has been shown to be reduced in schizophrenia. Previous studies have successfully established a method to generate reliable MMNs and have demonstrated the involvement of the NMDAR in the genesis of MMN (102, 103). Computational model was created to explain the observed functional MRI (fMRI) time-series data by using a state-space model (104), and has been used to model the

evoked components as measured by electroencephalography (EEG) or magnetoencephalography (MEG), that has been used to study the production mechanisms of MMN and P300 (103).

Building a computational model for MMN may be helpful for exploring the network of MMN in schizophrenia and its treatment by the NMDAR enhancers such as D-serine (105). Longitudinal studies have also shown that MMN recordings can assist in predicting the conversion from the prodromal phase to psychosis (106).

DDAO INHIBITION FOR SCHIZOPHRENIA

D-serine is more potent than other NMDAR co-agonists as the neurotransmitter for the glycine-site of the NMDAR (107). DAAO, a flavoenzyme of peroxisomes existing in the brain, kidney and liver of mammals, is responsible for degrading D-serine, D-alanine, and other D-amino acids. Therefore, one of the avenues to enhance NMDAR function is via inhibiting DAAO activity.

Sodium benzoate, a DAAO inhibitor, can elevate synaptic concentrations of D-amino acids, like D-serine and D-alanine, and thereby enhance NMDA neurotransmission. Previous clinical trials have studied the potential of sodium benzoate as an adjuvant therapy for schizophrenia. The first clinical trial suggested that sodium benzoate is beneficial in improving the clinical symptoms including positive and negative symptoms, cognitive and global functioning and quality of life in patients with chronic schizophrenia (40). The effect size of sodium benzoate treatment for Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint was 1.76, which was much higher than the effect size (0.51) of sarcosine adjuvant therapy for the PANSS total score in patients with chronic schizophrenia (108).

GLUTAMATERGIC MODULATORS IN PATIENTS WITH PERSISTENT PSYCHOTIC SYMPTOMS

Only a minority of patients with first-onset schizophrenia return to their original level of functioning. Among individuals who respond poorly to antipsychotics (which are principally dopamine antagonists), their glutamatergic/NMDAR dysfunction may lead to failures by the treatment. While second- and third-generation antipsychotics are increasingly used, therapy for refractory schizophrenia remains a great challenge. Even with the treatment of clozapine (the last-line therapy for schizophrenia), a substantial portion of patients still suffer from persistent psychotic symptoms. However, after many clinical trials with various agents, including diverse glutamatergic modulators, there is no convincing evidence to demonstrate the efficacy of adjuvant therapy for clozapine-resistant patients (109). In a recent study, sodium benzoate even showed a beneficial effect on positive and negative symptoms and quality of life with the dose of 2 g/day in patients with clozapine-resistant schizophrenia (43).

STRATEGIES OF EARLY DETECTION AND INTERVENTION OF PRODROMAL SCHIZOPHRENIA

The prodromal phase of schizophrenic disorders has been recognized since the Nineteenth century (110). Recently, the Criteria of Prodromal Syndromes (COPS) diagnostic criteria have been applied; there are three operationally defined prodromal syndromes: attenuated positive psychotic symptom syndrome, brief intermittent psychotic syndrome, and genetic risk and recent functional decline syndrome (18, 111, 112). The PRIME prodromal research team in Yale University has also developed a semi-structured interview called the Structured Interview for Prodromal syndromes (SIPS) (113). The SIPS is utilized to rate presenting symptomatology and to determine if COPS criteria are met. The Scale of Prodromal Symptoms (SOPS) (114), embedded in SIPS, is a 19-item scale designed to measure the severity of prodromal symptoms. The SOPS contains four subscales: five positive, six negative, four disorganization, and four general symptom items. The detection and intervention of young people in the prodromal phase is a newly developed area in psychiatry (115), and the ethical considerations about treatment options must be treated with sensitivity (116).

Standard guidelines have been used in our previous studies aiming to establish or examine prodromal or ultra-high-risk (UHR) (112), clinical high risk (117), and 5 at-risk mental state (118). Recently, objective strategies have been emphasized for screening prodromal illness in many studies. The fMRI with magnetic resonance spectroscopy (MRS) is one of those that identify early stage of mental illness. Individuals with prodromal symptoms demonstrated smaller differential activation in frontal regions in fMRI data (119).

The possibility of treatment intervention during the prodromal phase has a history almost as long as it was first identified (120). Both typical and atypical antipsychotics, including risperidone and olanzapine, have been utilized to reduce prodromal symptoms or the risk of progression to schizophrenia (121–123). However, safety and side effect concerns exist; and it remains unclear whether the benefits of antipsychotic treatments outweigh the risks (116).

Therefore, there is an urgent need to develop safer interventions for schizophrenic prodrome. D-serine (124) and fish oil (79) have been demonstrated to be beneficial as treatment of prodromal schizophrenia. Other antioxidants such as glucoraphanin have also shown potential in preventing the onset of psychosis in the adult offspring after maternal immune activation (125). Future trials with glutamate modulators or antioxidants in early psychosis and even prodromal schizophrenia should consider biomarker-guided treatment (16).

SUMMARY

It is generally recognized that intervention of early psychosis and prevention the progression of schizophrenic prodrome to full-blown schizophrenia is essential, in order to avoid subsequent

functional deterioration. Current antipsychotic medications have not yet been approved for such populations mainly due to the lack of overt efficacy and various side effects including metabolic syndrome and hyperprolactinemia. Therefore, developing novel antipsychotic drugs with better efficacy and safety is critical. Compounds that can enhance the NMDAR have shown encouraging efficacies with favorable safety profiles in clinical trials for patients with schizophrenia. It will be valuable to test whether NMDAR enhancers are beneficial for patients with earlier phases of psychosis.

Identifying high risk populations who are prone to develop full-blown psychosis would be very helpful to apply early an intervention strategy to those people who are in need. It is important to search for biomarkers representing the pathophysiology of schizophrenia and more importantly, the biological changes in the process of early psychosis. In addition to dopamine hypothesis, dysfunction of glutamate signaling, and dysregulation of oxidative stress have been considered to play important roles in early psychosis and schizophrenic prodrome. It will be interesting to search for potential biomarkers that

are related to glutamate and oxidative stress modulations via blood-based or brain imaging approaches.

Combining biomarkers and novel drug development for early psychosis is critical in future studies. Notably, the intervention that can both treat early psychosis and serve as the biomarker might have more potential to reach the goal.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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