Review

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Positive allosteric modulators of metabotropic glutamate 2 receptors in schizophrenia treatment

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The past two decades have witnessed a rise in the 'NMDA receptor hypofunction' hypothesis for schizophrenia, a devastating disorder that affects around 1% of the population worldwide. A variety of presynaptic, postsynaptic, and regulatory proteins involved in glutamatergic signaling have thus been proposed as potential therapeutic targets. This review focuses on positive allosteric modulation of metabotropic glutamate 2 receptors ($mGlu_2Rs$) and discusses how recent preclinical epigenetic data may provide a molecular explanation for the discrepant results of clinical studies, further stimulating the field to exploit the promise of $mGlu_2R$ as a target for schizophrenia treatment.

Schizophrenia: limitations with currently available drugs

Schizophrenia is a chronic debilitating mental disorder that affects approximately 1% of the general population. Symptoms vary from patient to patient but are generally categorized into positive (e.g., hallucinations, delusions, and disorganized speech and behavior), negative (e.g., social withdrawal, lack of motivation, flat affect), and cognitive (e.g., impairments in memory, attention, and executive function). These symptoms are typically associated with social and/or occupational dysfunction. Although the natural course is heterogeneous, the illness typically strikes in late adolescence or early adulthood and usually continues throughout life [1,2]. The prognosis of patients is also variable, but is often poor, with high rates of unemployment, homelessness, violence, and suicide [3,4]. Given the combination of onset in early adulthood and the chronic course, schizophrenia presents a staggering drag on the economy and society. It has been estimated that the cost of schizophrenia in the USA in 2002 exceeded $62 billion [5] and the World Health Organization ranks this disorder among the top 10 causes of disability in developed countries [6].

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The classical dopamine (DA) hypothesis (see Glossary) has dominated the theories of schizophrenia since the mid-20th century after the observation that first-generation, or 'typical', antipsychotic drugs, such as chlorpromazine and haloperidol, are high-affinity antagonists of dopamine D_2 receptors. Hyperactivity in the mesolimbic DA pathway was originally proposed to underlie positive symptoms of schizophrenia [7]. While effective against positive symptoms, typical antipsychotic drugs demonstrate limited efficacy against negative symptoms and cognitive impairments which have been shown to contribute to functional impairment and predict poor prognosis [8]. Moreover, these

Glossary

Allosteric site: a binding site on a receptor macromolecule that is non-overlapping and spatially distinct from, but conformationally linked to, the orthosteric binding site.
Dopamine (DA) hypothesis: the most classical schizophrenia hypothesis that attributes psychotic symptoms to hyperactive DA signaling in the brain.
Epigenetics: literally means 'above' or 'on top of' genetics. It refers to external modifications to DNA that turn genes 'on' or 'off' without changes in DNA sequence.
Excitatory postsynaptic potential (EPSP): a temporary depolarization of postsynaptic neuron membrane potential that makes it more likely that this neuron will trigger an action potential.
Glutamate: the main excitatory neurotransmitter in the brain.
G-protein-coupled receptor (GPCR): an integral plasma membrane protein that senses molecules outside the cell and transduces those extracellular signals to intracellular relay proteins, the heterotrimeric GTP-binding proteins (G proteins).
Heteromer: structural assembly composed of two or more different components.
Histone: evolutionarily conserved proteins found in eukaryotic cell nuclei that package DNA into structural units termed nucleosomes. Covalent modifications at the N-terminal tail of histones correlate with open or closed states of chromatin, depending on the type of modification, and thus lead to changes in gene expression.
Histone deacetylase (HDAC): a class of enzymes that remove acetyl groups from histones, allowing the histones to wrap the DNA more tightly and repress gene transcription.
Metabotropic glutamate receptors (mGluRs): GPCRs that bind glutamate and function to modulate, rather than mediate, synaptic transmission. This is to differentiate them from 'ionotropic' glutamate receptors, such as NMDA receptors, which are ion channels mediating excitatory neurotransmission.
***N*-methyl-D-aspartate (NMDA) receptor:** a glutamate receptor and ion channel protein found in nerve cells. It is involved in synaptic transmission and plays an important role in learning and memory.
NMDA hypofunction hypothesis: a glutamate-based hypothesis which postulates that reduced NMDA glutamate receptor activation underlies the development of different schizophrenia symptoms.
Orthosteric site: the binding site on a receptor macromolecule that is recognized by the endogenous agonist for that receptor.

drugs are associated with several side effects, including hyperprolactinemia and extrapyramidal symptoms (EPS). The second-generation, or 'atypical', antipsychotic drugs were introduced into the clinical practice in the early 1990s in an attempt to improve clinical efficacy and decrease side effects. Second-generation drugs (such as clozapine, olanzapine, risperidone, and quetiapine), which have less potential to induce EPS or hyperprolactinemia, differ pharmacologically from the typical ones in that they have less affinity for D_2 receptors and higher affinity/functional interaction with other monoaminergic receptors, including the serotonin 2A receptor (5-HT_{2A}) [2,9]. Because of the dual dopamine–serotonin mechanism of action of atypical antipsychotic drugs, a serotonin hypothesis for schizophrenia was also proposed [10]. Although highly effective against a wider range of symptoms than typical agents, atypical antipsychotics still have modest efficacy against negative symptoms. In addition, recent clinical evidence does not support the notion that second-generation drugs are superior to first-generation in improving neurocognition [11]. Last but not least, atypical agents are associated with side effects, usually metabolic, and in rare cases severe, such as agranulocytosis seen with clozapine [2]. Despite the availability of many typical and atypical antipsychotic drugs, full functional remission is achieved in fewer than 35% of people with schizophrenia [12]. Moreover, most of the responders are 'partial responders' with whom negative and cognitive symptoms remain problematic, suggesting that impairment and/or dysregulation in DA and serotonin signaling cannot fully account for the underlying pathology. The limitations of the presently available drugs underscore the need for identification of new antipsychotic compounds aimed at new molecular targets. We focus here on positive allosteric modulation of $mGlu_2R$ as a promising therapeutic strategy to treat schizophrenia.

Glutamate and schizophrenia

To account for negative and cognitive symptoms of schizophrenia, the DA hypothesis was expanded to postulate hypoactivity in the mesocortical pathway as well. Despite this expansion, the DA hypothesis still likely oversimplifies the neurocircuitry of schizophrenia and does not explain why the mesocortical DA pathway will be hypoactive while the mesolimbic DA pathway is hyperactive. If anything, this dichotomy suggests that either DA is partially involved in the molecular underpinnings of schizophrenia, or alternatively that multiple defective neurotransmitter systems eventually converge on and disrupt the DA system [7]. In an attempt to account for the shortcomings of the DA hypothesis, the 'NMDA receptor hypofunction' hypothesis was proposed by Olney and Farber in 1995 [13] based on the observation that non-competitive NMDA antagonists such as phencyclidine (PCP) and ketamine induce a psychotomimetic state that closely resembles schizophrenia in healthy human individuals [14,15], and exacerbate preexisting symptoms in schizophrenic patients [16,17]. Although the pharmacology of cocaine and other amphetamine-like psychostimulants is complex [18,19], they share the ability to bind to dopamine transporters and increase synaptic levels of dopamine. Importantly, unlike amphetamine-like psychostimulants, glutamatergic PCP and ketamine dissociative drugs not only induce positive symptoms but also negative symptoms and cognitive dysfunction that better recapitulate the clinical syndrome of schizophrenia. Subsequently, PCP-like drug models have become widely employed in the search for novel treatments. It was proposed that defective NMDA receptors on cortical γ-aminobutyric acid (GABA) interneurons (Figure 1) render these interneurons less effective in inhibiting glutamate projection neurons that project to the ventral tegmental area (VTA). This disinhibition results in excessive glutamate tone, which now overstimulates the DA mesolimbic pathway giving rise to the positive symptoms. An alternative pathway that could be fundamental for cognition might be the functional crosstalk between NMDA and 5-HT_{2A} receptors in pyramidal neurons of prefrontal cortex [20]. Similarly, negative and cognitive symptoms may arise from NMDA receptor hypofunction. In this case hyperactive glutamate projection neurons overactivate GABAergic interneurons, located in the VTA, causing them to release excess GABA and overinhibit the mesocortical DA pathway that now becomes unable to adequately supply DA to the prefrontal cortex [7]. Thus, defective glutamate neurocircuitry might actually drive the excess DA in the mesolimbic pathway as well as the deficiency of DA in the mesocortical pathway. In addition, the resulting glutamate excitotoxicity might drive an ongoing neurodegenerative process responsible for the structural brain changes seen in schizophrenic brains on volumetric MRI [21,22], although the presence of neurodegeneration in schizophrenia remains controversial [23–27]. Interestingly, group II metabotropic glutamate

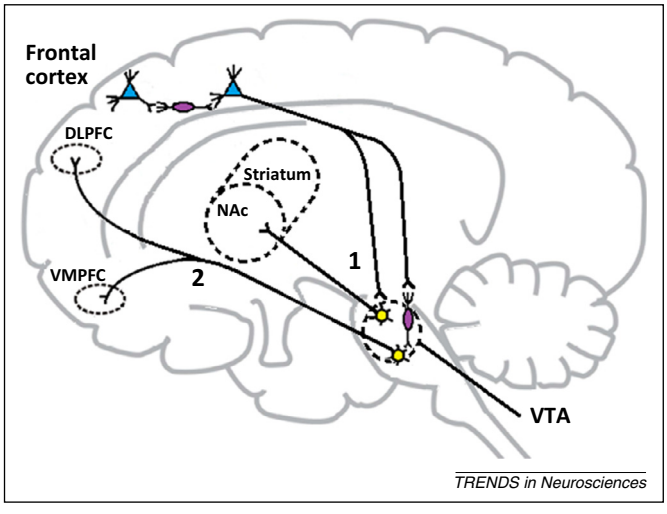

Figure 1. Glutamate neurocircuitry implicated in schizophrenia. Normally, cortical GABA interneurons (in purple) exert an inhibitory tone on glutamate neurons that project to the VTA. When optimal, this inhibitory tone controls the amount of glutamate released in the VTA, and subsequently the activity of the mesolimbic (**1**) and mesocortical (**2**) DA pathways. In schizophrenia, a defective NMDA receptor on the cortical GABA interneurons results in disinhibition of cortical brainstem glutamate projections. Excessive glutamate firing leads to overactivation of the mesolimbic DA pathway (1) and excessive release of DA in the nucleus accumbens. This might be responsible for development of positive symptoms in schizophrenic patients. Similarly, negative and cognitive symptoms may arise from NMDA receptor hypofunction. Hyperactive glutamate tone overactivates GABAergic interneurons in the VTA, overinhibiting the mesocortical DA pathway (2) that now becomes unable to adequately supply DA to the prefrontal cortex resulting in 'hypofrontality'. Abbreviations: DA, dopamine; DLPFC, dorsolateral prefrontal cortex; NAc, nucleus accumbens, VMPFC: ventromedial prefrontal cortex; VTA, ventral tegmental area.