

Reappraisal

When the drugs don't work: the potential of glutamatergic antipsychotics in schizophrenia

Evangelos Papanastasiou,* James M. Stone* and Sukhi Shergill

Summary

Currently available antipsychotic drugs target dopaminergic neurotransmission. Many patients do not respond fully to these treatments, and there has been considerable effort to investigate alternative targets. Here we summarise the rationale and recent evidence supporting efforts to develop glutamatergic antipsychotic drugs.

Declaration of interest

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Antipsychotics: should we look beyond D₂ antagonism?

In the 60 years since the antipsychotic properties of chlorpromazine were discovered, a large number of other drugs have been developed to treat psychosis. Despite differences in chemical structure, side-effects and toxicity, all currently available antipsychotics act as dopamine D₂ receptor antagonists.

Antipsychotic drugs induce full functional remission in fewer than 35% of people with schizophrenia.¹ In patients who show some response to D₂ antagonists, negative and cognitive symptoms are a particular problem, and generally seem to be refractory to antipsychotic treatment. Partial responders may have different neurochemical pathologies, and may therefore benefit from different treatment approaches. The glutamate system has been of particular recent interest as a target for novel antipsychotic drugs.² Here we summarise evidence for glutamatergic abnormalities in schizophrenia, and review recent clinical and preclinical findings concerning putative antipsychotic glutamatergic agents.

Glutamatergic neurotransmission – relevance to schizophrenia

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS), acting via ionotropic and metabotropic receptors. *N*-methyl-D-aspartate (NMDA) receptors (Fig. 1) are ionotropic glutamate receptors that have received particular interest regarding their involvement in psychosis. The uncompetitive NMDA receptor antagonists dizocilpine (MK-801), ketamine and phencyclidine (PCP), induce effects resembling the positive, negative and cognitive symptoms of schizophrenia in healthy individuals.³ Furthermore, they exacerbate similar symptoms in stable patients with schizophrenia.⁴

N-methyl-D-aspartate receptors open only in the presence of depolarisation of the cell combined with binding of both glutamate and glycine. The function of the NMDA receptor is crucial for the maintenance of a stable neuronal milieu, as it is the major Ca⁺⁺ gatekeeper. If the action of glutamate on the NMDA receptor is prolonged, excess Ca⁺⁺ enters the neuron, leading to excitotoxicity. The co-agonist glycine modulates NMDA receptor activity, with less risk of excitotoxicity. The glycine transporter-1 (GlyT₁) is primarily expressed in glial and neuronal

cells of the forebrain and has been of particular interest in the development of novel antipsychotic drugs.²

There has also been considerable interest in metabotropic glutamate receptors as targets for antipsychotic drugs – particularly mGluR_{2/3} receptors, which are presynaptic autoreceptors, and mGluR5 receptors, which are postsynaptic and positively modulate NMDA receptor function.²

The NMDA receptor hypofunction model of schizophrenia

The NMDA receptor hypofunction model of schizophrenia was first proposed by Olney & Farber.⁵ They reported that uncompetitive NMDA receptor antagonists led to neurotoxicity in rat brain regions closely resembling those affected by volume loss in patients with schizophrenia.⁵ They suggested that these changes were driven, in part, by cortical release of glutamate, a finding supported by microdialysis studies from other groups,⁶ and hypothesised that NMDA receptor antagonists lead to downstream release of glutamate by preferentially inhibiting GABAergic interneurons – leading to disinhibition of glutamate projection neurons. They suggested that individuals with schizophrenia may either have dysfunctional NMDA receptors, or GABAergic interneurons, leading to similar downstream effects.⁵

A number of lines of evidence add further support to this model. Recent analysis of genome-wide association studies has found that many genes implicated in schizophrenia converge on glutamate receptor signalling;⁷ patients with schizophrenia have been shown to have reduced binding to activated NMDA receptors in left hippocampus,⁸ a finding closely echoing post-mortem findings in patients with schizophrenia;⁹ and patients in the prodrome and first episode of psychosis have evidence of increased cortical glutamate transmission.¹⁰ We recently reported that individuals in a first episode of psychosis with a poor response to dopamine-blocking antipsychotic drugs have elevations in cortical glutamate levels compared with those who responded well to these drugs, supporting the hypothesis that poor responders may have a glutamatergic basis to their psychosis, and suggesting that it may be possible to identify individuals who are more likely to respond to glutamatergic agents at first presentation using scanning or other clinical biomarkers.¹¹

NMDA receptor modulation via the glycine site

In view of the toxicity of NMDA receptor agonists acting at the glutamate binding site, most drugs in development that have been

*These authors contributed equally to the work.

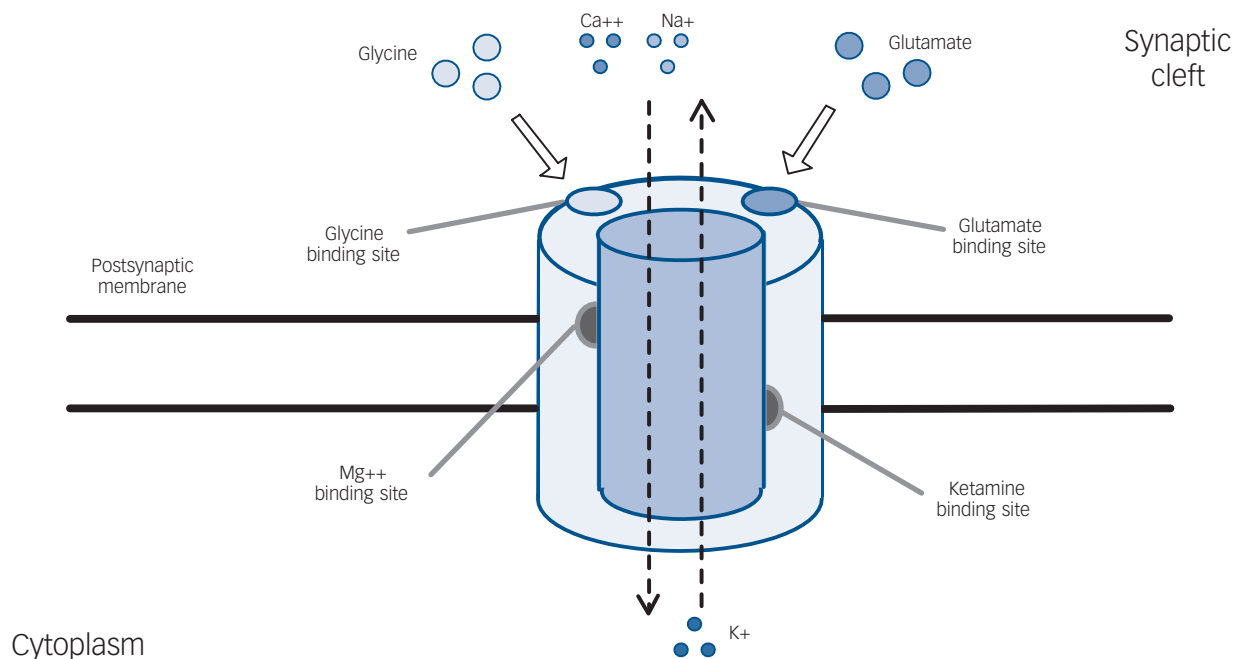


Fig. 1 An *N*-methyl-D-aspartate receptor.

designed to activate NMDA receptors either act as agonists at the glycine_B site, or aim to increase synaptic glycine concentrations through inhibition of GlyT1.¹² A number of pre-existing drugs that target the glycine_B site have already been tested as adjunctive agents in schizophrenia – including *D*-alanine, *D*-serine, glycine (glycine_B site agonists), *D*-cycloserine (glycine_B partial agonist), *N*-acetyl-cysteine (NAC, precursor to glutathione and NMDA receptor modulator), and sarcosine (GlyT₁ endogenous inhibitor). Although of relatively small effect size, many of these drugs show some efficacy in the treatment of refractory negative and cognitive symptoms of schizophrenia. When combined with non-clozapine antipsychotic agents, *D*-serine, NAC and sarcosine improved negative and total symptoms, whereas glycine reduced positive and total symptoms.¹³

Despite the small size of those trials, their encouraging results have stimulated interest by pharmaceutical companies in drugs targeting activation of the glycine_B receptor. It should be noted that the substances used in these trials were not developed for use as CNS drugs, and the doses required for a clinical response are high (30–60 g glycine per day has commonly been used). Drugs specifically designed to cross the blood–brain barrier and to target synaptic glycine transmission would be expected to have a cleaner effect with lower doses required. A variety of compounds have been patented and are presently undergoing clinical trials, in phases I, II and III.¹²

Metabotropic glutamate receptor agonists and positive allosteric modulators

Several pharmaceutical companies have been pursuing the development of drugs acting as positive modulators of metabotropic glutamate receptors – either agonists or positive allosteric modulators. A phase II clinical randomised controlled trial (RCT) compared LY2140023, a highly selective mGluR_{2/3} agonist for mGluR₂ and mGluR₃ receptors, with olanzapine and placebo in a total sample of 193 participants. The study demonstrated

significant improvements in both positive and negative symptoms of schizophrenia, with no associated increase in side-effects.¹⁴ However, a subsequent phase II clinical RCT, comparing various doses of LY2140023 with olanzapine and placebo, has not shown this positive benefit.¹⁵ The two studies using this compound were problematic in terms of placebo response – in the first published study there was no improvement in the placebo group, whereas in the second the placebo response was equal to the response to olanzapine. In addition, these studies targeted patients with chronic schizophrenia, whereas current evidence suggests that the glutamatergic abnormalities that mGluR_{2/3} agonists would be expected to address occur in patients in the early stages of illness.¹⁰ Findings are thus inconclusive at present, and future studies with this and related compounds are awaited with great interest.

As full agonists at metabotropic glutamate receptors have the potential to lead to receptor downregulation and neurotoxicity, there has been considerable interest in developing positive allosteric modulators of mGluRs, which should have less propensity for these effects. Positive allosteric modulators have been developed for mGluR₅, an mGluR_{2/3}, and have shown promising preclinical properties, but no clinical trial data have been published to date.²

The future

As there is no clear mechanistic understanding of the aetiology of psychosis, there is still a need for empirical studies to test the boundaries of our current theories. The focus in therapeutics is now broader than ever before, with a greater emphasis on cognitive and negative symptoms, and spread between a range of neurotransmitter systems, including the traditional focus on dopaminergic and serotonergic systems – partial dopamine agonists and multiple dopamine antagonists, 5-HT_{2C} and 5-HT₆ antagonists; the contemporary glutamatergic system – AMPAkinases, mGluR_{2/3} ligands and GlyT₁ inhibitors; intracellular signalling – PDE10a

inhibitors and histamine – H₃ antagonists.¹² One of the most promising avenues is the glutamatergic system, and GlyT₁ inhibitors offer a useful paradigm on enhancing the effects of existing antipsychotic efficacy. Given the complexity of the interactions between, and homeostatic mechanisms within, the different neurotransmitter systems, changes to NMDA receptor function may still be acting predominantly via the dopaminergic system. Although the pragmatic clinical trials are essential to evaluate new compounds, these also need to be accompanied by clinical studies providing data, testing the putative theoretical basis for each new drug – at present, functional and receptor imaging studies offer a promising avenue in this regard.

Evangelos Papanastasiou, MD, MSc, Department of Psychosis Studies, Institute of Psychiatry, King's College London; **James M. Stone**, BSc, MBBS, MRCPsych, PhD, Department of Experimental Medicine, Imperial College London, Hammersmith Hospital; **Sukhi Shergill**, BSc, MBBS, PhD, FRCPsych, Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK

Correspondence: Evangelos Papanastasiou, MD, MSc, Institute of Psychiatry, King's College London, Department of Psychosis Studies, CSI Lab, Box PO63, De Crespigny Park, Denmark Hill, London SE5 8AF. Email: evangelos.papanastasiou@kcl.ac.uk

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