NMDA glutamate receptors and how they are involved in schizophrenia

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1. Introduction to glutamate and its receptors

2. Evidence that NMDA receptors are involved in schizophrenia
But schizophrenia’s about dopamine?

**Normal**
- Prefrontal Cortex
- Limbic Sites
- Glutamate
- Dopamine neurons

**Schizophrenia**
- Prefrontal Cortex
- Limbic Sites
- Glutamate
- Dopamine neurons

*Arch Gen Psych* 1987;44:660-9
Glutamate synapses and receptors

70% of all neurons are glutamatergic (i.e. they release glutamate as their transmitter)

Glutamate is the main excitatory transmitter in the brain, and responsible for most signalling between one part of the brain and another

NMDA receptors are one of the three Classes of glutamate receptor

NMDA receptors are critical not only for neurotransmission, but also for neurodevelopment and neurotoxicity
The NMDA receptor

Both glutamate and a co-agonist have to bind to the NMDA receptor for the channel to open.

Each receptor is made up of several subunits: NR1 + NR2 +/- NR3 - and each subunit exists as 2 or more subtypes, so lots of scope for variation.
NMDA receptors in schizophrenia – lines of evidence

Basic notion = ‘NMDA receptor hypofunction’

- Glutamate and NMDA receptors crucial in brain development, plasticity, synaptic functioning, neural oscillations
- NMDA receptor antagonists (e.g. PCP, ketamine) produce or exacerbate psychosis
- NMDA receptor co-agonists (e.g. D-serine, glycine) improve some symptoms
- Enhancement of NMDA receptor function by other means also improves symptoms (e.g. mGlu agonists, glycine transporter inhibitors).
- Alterations in NMDA receptors in schizophrenia
- NMDA receptor mouse models ‘mimic’ schizophrenia
- Schizophrenia risk genes affect glutamate synapses
- Anti-NMDA receptor antibodies in some patients?
Recent Advances in the Phencyclidine Model of Schizophrenia

Daniel C. Javitt, M.D., Ph.D., and Stephen R. Zuckin, M.D.

Objective: Phencyclidine (PCP, "angel dust") induces a psychotomimetic state that closely resembles schizophrenia. As opposed to amphetamine-induced psychosis, PCP-induced psychosis incorporates both positive (e.g., hallucinations, paranoia) and negative (e.g., emotional withdrawal, motor retardation) schizophrenic symptoms. PCP-induced psychosis also uniquely incorporates the formal thought disorder and neuropsychological deficits associated with schizophrenia. The purpose of the present paper is to review recent advances in the study of the molecular mechanisms of PCP action and to describe their implications for the understanding of schizophrenic pathophysiology. Method: Twenty-five papers were identified that described the clinical dose and serum and CSF levels at which PCP induces its psychotomimetic effects. The dose range of PCP-induced effects were compared to the dose range at which PCP interacts with specific molecular targets and affects neurotransmission. Results: It was found that PCP-induced psychotomimetic effects are associated with submicromolar serum concentrations of PCP. At these concentrations PCP interacts selectively with a specific binding site (PCP receptor) that is associated with the N-methyl-D-aspartate (NMDA)-type excitatory amino acid receptor. Occupation of its receptor by PCP induces noncompetitive inhibition of NMDA receptor-mediated neurotransmission. Other NMDA antagonists such as the dissociative anesthetic ketamine induce PCP-like neurobehavioral effects in proportion to their potency in binding to the PCP receptor and inducing NMDA receptor inhibition. Conclusions: These findings suggest that endogenous dysfunction of NMDA receptor-mediated neurotransmission might contribute to the pathogenesis of schizophrenia. The relative implications of the PCP and amphetamine models of schizophrenia are discussed in relationship to the diagnosis and etiology of schizophrenia.

Transient impairment of NMDA receptors during development can have long-lasting effects
Schizophrenia genes and NMDA receptors

Many genes and gene variants increase risk for schizophrenia. Increasing evidence that these preferentially affect NMDA receptor signalling.

Assumption is that the risk variants impair some aspect of NMDA receptor function, either ongoing, or during brain development.
Schizophrenia: a genetic disorder of the synapse?
Glutamatergic synapses might be the site of primary abnormalities
Michael J Owen  professor of psychological medicine
Michael C O'Donovan  professor of psychiatric genetics
Paul J Harrison  professor of psychiatry

Six degrees of separation: on the prior probability that schizophrenia susceptibility genes converge on synapses, glutamate and NMDA receptors
PJ Harrison and VA West
Molecular Psychiatry (2006) 11, 981–983. doi:10.1038/sj.mp.4001886

Rare mutations in N-methyl-D-aspartate glutamate receptors in autism spectrum disorders and schizophrenia
J Torabozz2,3,4, O Kebir2,5, J Gauthier1, FF Hamdani4, L Xiong1, A Piton2, D Spiegelman2, É Hénaff1, B Millet4, S Zioutas1, C Heth1, A Joisher2, J Popot1, LE Delisi5, E Fontbonne1, L Motron1, N Forget-Guibou1, N Bovin1,3,12, J-Philippe1, P Drapeau3,4, R G Laffont5, GJ Rouleau1,10 and M-D Kréb3,13

Strong synaptic transmission impact by copy number variations in schizophrenia
Joseph T. Glessner,4, Murrebach P. Reilly,4, Cecilia E. Kim, Nagahide Takahashi, Anthony Albano, Cuiping Heu, Jonathan P. Bradfield, Haitao Zhang, Patrick M. A. Steinman, James H. Florey, Martin Insel, Eric Mostofsky, Edward C. Frackleton, Roccia Chiavacci, Kelly A. Thomas, Mathis Gijsen, Frederick G. O'Brien, Michael Davidson, Mark Weiser, Abraham Reichenberg, Kenneth L. Davis, Joseph J. Fried, Thomas P. Cappola, Kenneth B. Margulies, Daniel J. Rader,2,3,5,6,8,9, Kristina A. Giant, Joseph D. Buxbaum, Raquel E. Gur, and Hakon Hakonarson1,4,5,6

Functional gene group analysis identifies synaptic gene groups as risk factor for schizophrenia
ES Lips1, LN Cornelisse1, RF Toonen1, JL Min1, CM Hultman2,3, the International Schizophrenia Consortium1,9, PA Holmans2, MC O’Donovan2, SM Purcell2,3,7,6, AB Smith3, M Verhage1, PF Sullivan1,9, RM Visscher1 and D Posthuma1,2

De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia
Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial

Sandeep T Patil¹,¹³, Lu Zhang¹, Ferenc Martenyi², Stephen L Lowe³, Kimberley A Jackson⁴, Boris V Andreev⁵, Alla S Avedisova⁶, Leonid M Bardenstein⁷, Issak Y Gurovich⁸, Margarita A Morozova⁹, Sergey N Mosolov⁸, Nikolai G Neznarov¹⁰, Alexander M Reznik¹¹, Anatoly B Smulevich⁹, Vladimir A Tochilov¹², Bryan G Johnson¹, James A Monn¹ & Darryle D Schoepf¹,¹³

- No EPS, PRL, or weight gain
Summary

- NMDA receptors are important in schizophrenia.
- They contribute to its cause, via NMDA receptor-related genes.
- They are involved in the disease process, in various ways.
- They are potential (indirect) targets for treatment, and are likely to be the first non-dopamine drugs to reach the clinic.