Schizophrenia mechanistic model based on NMDA Receptors Hypofunction

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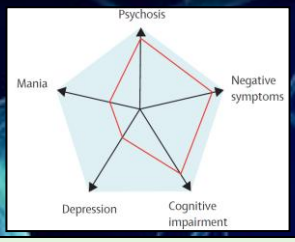
Introduction

Schizophrenia is a psychotic disorder with a prevalence of 1% and three kinds of symptoms:

- Positive: additional to normal experience. Hallucinations, delusions.
- Negative: lack of normal experience. Depression, social withdrawal.
- Cognitive: memory and attention alterations, concept disorganization.

Brain changes are also observed, although they are not specific so they can't be used for diagnosis. The heritability is high (80%), due to some genetic or epigenetic changes. There are also environmental risk factors, during both fetal and pre-adult life.

Treatment is focused on blocking dopamine receptors, but antipsychotics are only effective against positive symptoms and cause metabolism or motor side effects, so investigation in schizophrenia-related brain mechanisms is important for the design of new treatments.



Scores of an hypothectical schizophrenic patient in different symptoms

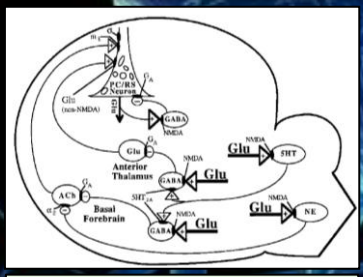
Hypothesis

The aim of this review is to define the new schizophrenia hypothesis and, considering the supporting evidence, draw conclusions. This hypothesis states that schizophrenia could be caused by a NR dysfunction and its downstream effects.

Methodology

Studies and reviews found using the Pubmed database were used for the review; the search included keywords such as "Schizophrenia", "NMDA receptors" or "treatment". Also, Neurochemistry biography was used to acquire a basis of knowledge in biochemistry of the brain.

Mechanistic model



Feedback regulation of the excitatory system

Exposure to NR antagonists (PCP, ketamine) induce schizophrenia-like symptoms, much more similar than the ones produced by dopaminergic drugs, especially in chronic exposures; revealing NR importance.

Glutamate works as an excitatory agent, but also as a main regulator of inhibitory tone. Glutamate-NR interaction activates parvalbumin-positive GABAergic interneurons, which inhibit the principal excitatory pathways of the limbic and cortical regions. NR blocking would eliminate this regulation and generate an excessive stimulatory stimulus causing morphologic changes in postsynaptic neurons. Afterwards, compensatory systems would diminish the brain activity. These morphological changes, taking place during the brain development, could be responsible for adult schizophrenia symptoms and also some neurodegeneration. PFC, responsible for personality, decision making, adequacy of social behaviour, etc. is especially affected: parvalbumin levels, metabolic activity and the number of GABAergic axon terminals are lower than usual in patients' PFC.

Evidence

Administration of NR antagonists.

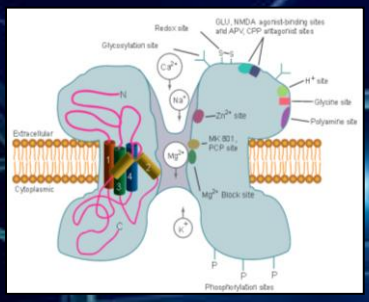
i. Early administration in rats increases neuronal death and modifies adult animals' behaviour: hyperlocomotion, stereotyped behaviour, alteration of social and cognitive functions.
ii. Acute administration in rats increases neurotransmitters' extracellular concentration and generates schizophrenia-like behaviour. Chronic administration is a better model: the effects are persistent, and metabolic changes, lesser neuronal density and adaptation mechanisms are also observed.
iii. Positive and negative symptoms are observed after ketamine administration to healthy humans. In patients, also hallucinations and psychosis. Chronic consumers have showed alterations in cognition.

NR importance.

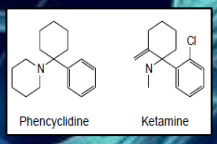
NR1 knock-out mice die immediately after birth. Mice with hypomorfic NR1 show schizophrenia-like behaviour. NR1 knock-out in excitatory neurons of PFC led to only cognitive symptoms, while in interneurons it caused all symptoms. Point mutations in the glycine binding site or knock-out of NR2 induce some but not all symptoms.

GABAergic system implication.

In patients: reduction of GABAergic innervations and alteration of $GABA_A$ receptors in PFC pyramidal neurons. NR antagonist administration also reduces the GABAergic activity.



NMDA receptor, its union sites and antagonists



Objections

Why would a deregulation during the development cause an illness that doesn't start until late adolescence? Because the mechanism altered by NR blocking affects processes and neuronal connexions that don't exist until the end of adolescence. The activation of the hyperglutamatergic state due to the brain maturation will cause the prodromal phase pre-symptoms that could trigger a psychotic episode. Evidence: administration of ketamine would cause psychotic reactions in human adults but not in pre-adults.

Causes of NR hypofunction

GENETIC

Polymorphisms in some genes have been associated to schizophrenia risk.

- ErbB2: neuregulin-1 receptor, controlling NR's kinetic properties.
- Dysbindin-1: associated to NR, implication in signalling.
- G72/G30 complex: regulates the co-agonist D-serine degradation.

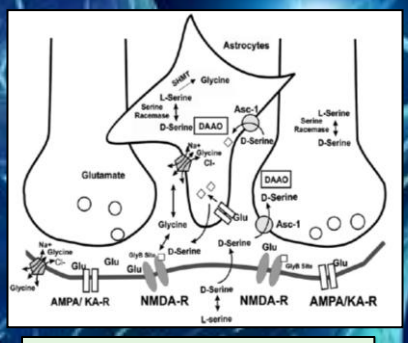
Alterations in transcription or translation of NR subunits or associated proteins could also be a cause.

NOT GENETIC

During synaptogenesis (3rd semester of pregnancy) neurons are extremely sensitive to glutamate stimulation.

- Too much stimulation (hypoxia) leads to excitotoxicity.
- Not enough stimulation (due to NR antagonists) activates apoptosis.

Therapies based on the hypothesis



The regulation of Glycine and D-serine extracellular levels.

Difficulty: the brain changes causing schizophrenia have already taken place, so they can't be avoided once the symptoms have started.

Permanent stimulation of NR using agonists is not a solution: it could cause excitotoxicity. Allosteric modulation seems a safer approach. **Glycine** and **D-serine** modulate GlyB site, on NR1 subunit. Their extracellular concentration is controlled by some transporters which have been found altered in patients. Daily administration of Glycine and D-serine to patients has resulted in improvement. The dose must be controlled to avoid side-effects: activation of Glycine R or NR internalization.

Acamprosate is used to avoid relapse in alcoholic patients. It normalizes glutamate release and NR function without disturbing the whole glutamatergic neurotransmission; by acting on GluR5-depending regulation. The treatment seems effective, even in prodromal phase.

Conclusions

1. Genetic or environmental alteration of NR function causes schizophrenia symptoms.
2. The cause is the lack of GABAergic regulation of the excitatory system.
3. NR blocking alters the dopaminergic neurotransmission: association to old hypothesis.
4. Development alterations have its consequences in late adolescence, after brain maduration, so symptoms appear in early adulthood.
5. Therapies based on this hypothesis have proved to be effective.

References

- Schultz, S.H.; North, S.W.; Shields, CG. 2007. "Schizophrenia: A Review". American Family Physician, 2007 Jun 15; 75(12): 1821-1829.
- Siegel, G.J.; Albers, R.W.; Brady, S.T.; Price, D.L. 2006. "Basic Neurochemistry: mollecular, cellular, and medical aspects" 7th edition. Burlington, Massachussets, Elsevier Academic Press, cop.
- Bickel, S; Jaitt, Daniel C. 2009. "Neurophysiological and neurochemical animal models of schizophrenia: focus on glutamate". Behavioural Brain Research 204, 352-362.
- Olney, John W; Newcomer, John W; Farber, Nuri B. 1999. "NMDA receptor hypofunction model of schizophrenia". Journal of Psychiatric Research 33, 523-533.