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 early life and adulthood.

**Treatments** 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.

**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 bibliography was used to acquire a basis of knowledge in biochemistry of the brain.

**Mechanistic model**

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**

**NMDA receptor, its union sites and antagonists**

- Glutamate: L-glutamic acid, excitatory agent.
- NR antagonist: PCP, ketamine.
- Glycine: NR modulator.
- Ketamine is a NR antagonist.

**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 connections 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.

**Therapies based on the hypothesis**

- **Acamprosate**
- **D-serine**
- **Glycine**

- Acamprosate: GLU antagonist. It is a glutamate modulator that acts at the NMDA receptor. It is used to prevent relapse in alcoholics. It normalizes glutamate release and NR function without disturbing the whole glutamatergic neurotransmission; by acting on GluR5-containing receptors.
- D-serine: GLU agonist. It 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-containing receptors.
- Glycine: GLU modulator. It is used to prevent relapse in alcoholic patients. It normalizes glutamate release and NR function without disturbing the whole glutamatergic neurotransmission; by acting on GluR5-containing receptors.

**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 maturation, so symptoms appear in early adulthood.
5. Therapies based on this hypothesis have proved to be effective.

**References**