SCHIZOPHRENIA: State of the art

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Introduction

Schizophrenia has been described as "one of the worst disease affecting mankind". Because of the pervasiveness of associated deficits and frequently long-life course, it is among the top ten leading causes of disease-related disability in the world.
Estimates of the risk of developing schizophrenia over one's lifetime ranges from 0.3 to 2.0% with an average of approximately **0.7%**.
The median age of onset is about 23 years in men and 28 years in women.

Schizophrenia's **symptoms** can be divided in:

- **Positive symptoms**: delusions, hallucinatory experiences and bizarre behavior.
- **Negative symptoms**: blunted or flat affect, poor rapport, passive/apathetic social withdrawal, stereotyped thinking or alogia
- **Cognitive symptoms**: conceptual disorganization and formal thought disorder.

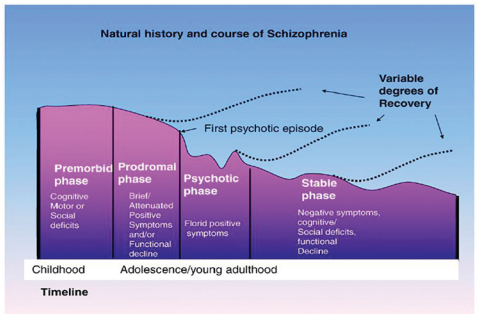

Figure 1. Evolution of schizophrenia with phases of illness. Prodromal phase: certain signs and symptoms are present. Psychotic/active phase: multiple psychotic episodes with brief periods of being free of symptoms. Stable/Chronic phase: patients do not appear psychotic but may experience some negative symptoms. Ref. 1

Etiology

Genetic Factors

GENES	PROTEIN FUNCTION	REFERENCE
NRG1/ERBB4	Nrg1 interacts with ErbB4 and controls the allocation of normal numbers of PV⁺ interneurons in the cerebral cortex. Also they play a role in the wiring of cortical inhibitory circuits.	Ref. 2
DTNBP1	Dysbindin is important for neuromuscular synapse formation and maintenance. Its mRNA expression has been shown to be reduced in schizophrenic patients	Ref. 3
DRD1-4	Dopamine receptor 2 antagonists are the only empiric pharmacological treatment available for schizophrenia. For that reason, dopamine receptor genes have always been a primary target for schizophrenia heritability.	Ref. 4
DISC1	Scaffolding protein widely expressed on the brain with multiple functions during brain development and in the adult brain. One of these functions would be the regulation of the normal functioning of cortical PV⁺ interneurons.	Ref. 5
COMT	Enzyme that degrades catecholamines such as dopamine, epinephrine and norepinephrine.	Ref. 4

Table 1. Examples of genes that have been linked to schizophrenia and the function of their product proteins.

Environmental Factors

	ENVIRONMENTAL FACTOR	DESCRIPTION	REFERENCE
PRENATAL	**Nutrition**	Prenatal nutrition deprivation,, elevated homocysteine in mothers, prenatal vitamin D deficiency.	Ref. 6 Ref. 7 Ref. 8
PRENATAL	**Infection**	Exposure to influenza, rubella, *Toxoplasma gondii*, HSV, CMV.	Ref. 9
PRENATAL	**Pregnancy and birth complications**	Obstetric perinatal complications, severe stress during first trimester.	Ref. 10 Ref. 11
PRENATAL	**Advanced paternal age**	Older paternal age.	Ref. 12
POSTNATAL	**Migrant status**	First and second generation migrants.	Ref. 13
POSTNATAL	**Urbanicity**	Urban place of birth, population grown up in urban places.	Ref. 14
POSTNATAL	**Cannabis use**	Use of cannabis during adolescence.	Ref. 1

Table 2. Environmental factors that play a role in the etiology of schizophrenia.

Material and Methods

Literature research using mainly two search engines: PubMed and Sciencedirect. The parameters sought were:

- Schizophrenia.
- Schizophrenia, marking the following categories: Review, Clinical Trial, Meta-Analysis, Randomized Controlled Trial.

Consulting dictionaries and books on the subject.
Schizophrenia Research magazine, available on-line at UAB catalog.

Pathophysiology and actual research pathways

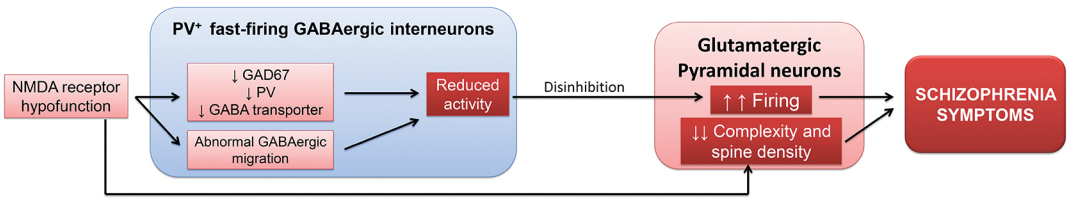

Figure 2. Scheme showing the actual state of the art of schizophrenia's pathophysiology

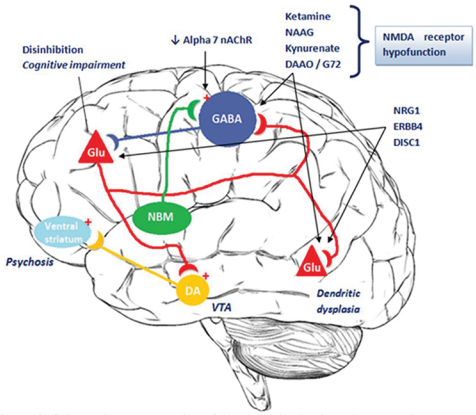

Figure 3. Schematic representation of the synaptic circuitry relevant to the pathophysiology of schizophrenia.

Figures 2 and 3 show a brief summary of current knowledge about schizophrenia's pathophysiology.
NMDA receptor hypofunction leads to:

- Downregulation of GABA-related metabolism proteins in PV⁺ fast-firing GABAergic interneurons
- Abnormal GABAergic interneuron migration
- Reduction in complexity and spine density in Glutamatergic Pyramidal neurons.

The first two events cause a disinhibition of the pyramidal neurons causing an increase of the firing.
All these facts cause schizophrenia-like symptoms in animals and are believed to be the main causes of the disease.

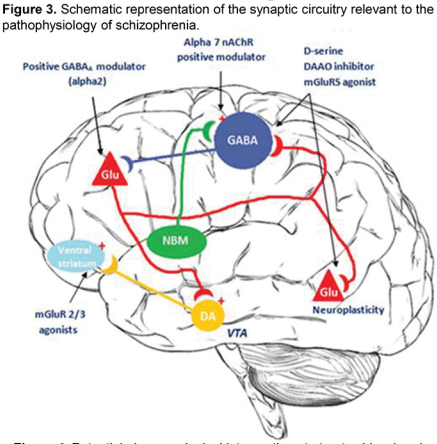

Figure 4. Potential pharmacological interventions to treat schizophrenia.

TARGET	ACTION	CONSEQUENCE
Glycine Modulatory Site (GMS - NMDA)	Administration of GMS agonists to increase its saturation.	Enhance activation of NMDA receptors.[15]
D-serine / DAAO (NMDA)	Inhibitors of DAAO. Improve Serine racemase performance.	Increase D-serine in the brain, increasing GMS occupancy and activation of NMDA receptors. [15]
Nrg1 / ErbB4	Research the pathway and functionality of these proteins involved in GABAergic interneuron migration.	Improved migration during development of GABAergic interneurons and better synapse formation with pyramidal neurons.[2]
DISC1 / DTNBP1	Research the pathway and functionality of these proteins involved in PV⁺ GABAergic interneuron functionality.	Compensate the malfunctioning of PV⁺ GABAergic interneuron s.[3,5]
Group II mGluRs	Administration of mGlur II agonists	Reduction of glutamate release by pyramidal neurons (antipsychotic action).[16]
GABA$_A$ receptors	Administration of benzodiazepine-like selective compound for GABA$_A$ receptors containing α-2 or α-3 subunits.	Improved cognitive functions and gamma oscillations.[17]
α7nAChRs (Cholinergic receptors)	Administration of α7nAChRs positive modulators.	Improved learning and memory.[18]

Table 3. Potential targets for research in schizophrenia. Possible treatment actions and consequences in the course of the disease.

Treatment

There are two types of antipsychotics, first-generation or typical antipsychotics, and second-generation or atypical antipsychotics. All of them affect postsynaptic dopamine receptors (D_2) but a distinguishing feature of second-generation antipsychotics is that they produce fewer extrapyramidal side effects (EPS) than the first-generation drugs.

1st Generation	Chlorpromazine, Haloperidol
2nd Generation	Clozapine, Olanzapine, Risperidone

Table 4. Examples of antipsychotics.

Conclusions

- We are still not capable of integrating all the knowledge about schizophrenia in a whole theory, making it difficult to find an effective treatment.
- Advances in the subject are increasingly encouraging thanks to the efforts of multidisciplinary teams.
- It is extremely important to keep supporting schizophrenia research so that in a few years or decades we may be able to get rid of one of the worst diseases affecting mankind.

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