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Theories of the pathogenesis of schizophrenia

Justyna Dąbrowska[1]*, Magdalena Wójcik[1], Julita Szarpak[1], Damian Bator[1], Joanna Milanowska[2], Hubert Nieścior[1]

(1) Student Science Club at the Department of Applied Psychology, Medical University of Lublin
(2) Department of Applied Psychology, Medical University of Lublin
* E-mail address: jdabrowska00@gmail.com

ORCID ID:
Justyna Dąbrowska https://orcid.org/0000-0002-1356-6965
Magdalena Wójcik https://orcid.org/0000-0002-0999-6284
Julita Szarpak https://orcid.org/0000-0002-5091-0235
Damian Bator https://orcid.org/0000-0002-8464-932X
Joanna Milanowska https://orcid.org/0000-0001-9741-1583
Hubert Nieścior, https://orcid.org/0000-0002-4709-4396

Abstract

Introduction: Schizophrenia is one of the most serious and frightening of all mental illnesses. It affects almost 1% of the population worldwide. The main concept and treatment of schizophrenia are based on the dopaminergic hypothesis. However, accumulating evidence has shown that the core pathophysiology of schizophrenia might involve dysfunction in dopaminergic, glutamatergic, serotonergic, and gamma-aminobutyric acid signaling.

The aim of the study: The purpose of this systemic review was to collect and analyse current and new information on the pathogenesis of schizophrenia.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed database was carried out using the following keywords: schizophrenia, dopamine hypothesis, serotoninergic hypothesis, hypothesis of schizophrenia .

Description of the state of knowledge: There are evidence that pathogenesis of schizophrenia include dysfunction in dopaminergic, serotoninergic, GABAergic, glutamatergic systems. The use of drugs that act on any of these systems reduces the symptoms of the disease. Nicotinic receptors may also be the target for drugs in treatment of schizophrenia. Studies about the role of nicotinic receptors in pathogenesis of schizophrenia show that it normalize many of the sensory processing deficits found in schizophrenia.

Summary: Despite the fact that current concept and treatment are still based on the dopaminergic hypothesis of the disease, existing theories and each new theory, open up different ways for treating schizophrenia. Considering that schizophrenia is one of the most serious and frightening of all mental illnesses and has major public health implications, more research about pathogenesis and ways of treatment is needed.

Key words: schizophrenia, dopamine hypothesis, serotoninergic hypothesis, hypothesis of schizophrenia

1. Introduction

Schizophrenia is a complex, heterogeneous behavioral, cognitive syndrome and one of the most serious and frightening of all mental illnesses. The name schizophrenia comes from the early observation that the disease is characterized by "disconnection or disruption of mental functions" [1]. The disease typically appears in late adolescence or early adulthood. It affects up to 1% of the population. The pathomechanism of schizophrenia is not fully understood and current antipsychotics are characterized by severe limitations [2]. It has major public health implications - in England schizophrenia costs society £11.8 billion per year with around a third of this accounted for by direct expenditure on health and social care, provided both in hospitals and the community [3].

2. Symptoms of schizophrenia

Schizophrenia typically presents in early adulthood or late adolescence. It appears earlier in men than in women. Men have also tend to experience a more serious form of the illness with more negative symptoms, less chance of a full recovery, and a generally worse outcome [4]. It is also more frequent in people born in cities [5]. Environmental and social factors have an important role in development of schizophrenia, for example the risk of schizophrenia in migrants is greatest when they form a small proportion of their local community [6].

In schizophrenia, we can found three groups of symptoms – positive, negative and cognitive. Definition of symptoms of schizophrenia [7,8] (Tabl. 1):

Table 1

Positive symptoms

Lack of insight	Failure to understand that symptoms are not real or caused by disease
Delusions	• Persecution - Patients think they are victims of some form of threat or are critical to the plot • Passivity - patients think that their thoughts or actions are being controlled by an external force or person • Others - delusions can develop around any topic; for example, impressive, sexual, or religious
Hallucinations	Perception without stimulus. It can be touch, smell, taste, or vision hallucinations. Auditory hallucinations are the most common.
Thought disorder	An inability to use language in a logical and consistent manner. “Knight move" - thoughts go in one direction, but suddenly depart at right angles, like a knight in chess, without a logical chain of thoughts.

Negative Symptoms

Avolition-apathy	Amotivation, anhedonia, asociality
Diminished expressiveness	Verbal and nonverbal

The positive symptoms of schizophrenia tend to relapse and resolve, however some patients experience residual, long-term psychotic symptoms. The negative and cognitive symptoms are usually chronic and are associated with long-term effects on social function. Psychosis appears usually in late adolescence or early adulthood. It can be preceded by a prodromal phase [9,10].

3. Pathogenesis of schizophrenia

3.1 Dopamine hypothesis

In the 1960s the dopamine hypothesis was proposed, due to the first antipsychotic chlorpromazine was found to successfully treat the positive symptoms of patients with schizophrenia. Since then, the development of newer antipsychotics has generally been consistent with the dopamine hypothesis. Use of dopamine antagonists, especially dopamine D2 receptor antagonists normalize increased dopaminergic activity, that is present in people with schizophrenia [11]. The dopamine D2 receptor is a G protein-coupled receptor, all antipsychotic drugs in use today block DA D2 receptors at clinically effective doses [12]. However, a dopamine receptor antagonist is not clinically effective at treating cortical-related symptoms, such as cognitive deficits, in schizophrenia.

There are several mechanism, that may be responsible for cognitive deficits, such as deficits in cortical dopamine function, dysfunction in the NMDA receptor or synaptic elimination. However, etiology of cognitive deficits is remains largely unknown [13,14,15]. Molecular imaging studies have supported an association of increased subcortical dopamine transmission with the positive symptoms of schizophrenia, with the limitation that this finding is not pathognomonic [16]. Early post-mortem studies suggested that the neuropathological changes in schizophrenia included both an increase in striatal dopamine levels, and an increase in D2 receptor density [17]. Recent research has shown tyrosine hydroxylase, the rate-limiting enzyme involved in the synthesis of dopamine, is significantly increased in the substantia nigra of patients with schizophrenia compared to patients with depression and healthy controls [18]. The hypothesis that D2 receptors are somehow altered in schizophrenia is supported by recent genome-wide association studies [19].

3.2 Glutamatergic Hypothesis

Glutamate is main excitatory neurotransmitters and the most common neurotransmitter in the brain [20]. The important glutaminergic pathways in schizophrenia are pathways linking to the cortex, the limbic system, and the thalamus regions [21]. Disturbances in the glutamatergic neurotransmission may influence mainly NMDA receptor functioning. NMDA receptors belong to ligand-gated ion channels, and are important for excitatory neurotransmission, excitotoxicity and plasticity [22,23]. Antagonists of NMDA receptor, such as ketamina can cause similar symptoms as in patients with schizophrenia [24]. In post mortem studies, some disturbances in glutamatergic receptor density and subunit composition in the prefrontal cortex, thalamus, and temporal lobe were found [24]. Morphological and structural brain changes, which may be caused by NMDA receptor hypofunction, can result in the development of psychosis [25,26]. Antipsychotics interacting with dopamine D2 receptor increase the phosphorylation of the NR1 subunit of the NMDA receptor, and thus enhance its activation and, consequently, gene expression [27]. Proton Magnetic Resonance Spectroscopy (1H-MRS) has been used to measure glutamate and glutamine levels in individuals at high risk of psychosis, as well as patients with first episode psychosis and chronic schizophrenia. 1H-MRS studies in schizophrenia have generally found that individuals with clinical or familial risk, and those with first episode psychosis have increased glutamine in anterior cingulate cortex [28,29]. On the other hand patients with chronic schizophrenia have normal or reduced cortical glutamate and glutamine levels [30]. There are several evidences to support glutamatergic hypothesis, nevertheless there are a number of potential limitations to the theory. The use of 1H-MRS as the primary tool for the in vivo imaging of the glutamatergic system has some limitations. In particular 1H-MRS may not be able to recognize intra and extracellular compartments. Changes could reflect alterations in either compartment [31].

3.3 Serotoninergic hypothesis

The mechanism of action of the hallucinogenic drug lysergic acid diethylamide was the basis for the development of the serotonergic theory of schizophrenia [32]. Overload of serotonin from the dorsal raphe nucleus resulting from stress may be responsible for disturbed activity of cortical neurons in schizophrenia [33].

There are reports that prolonged stress may trigger serotonergic overload in the cerebral cortex (mainly in anterior cingulate cortex and dorsolateral frontal lobe) [34]. There is not much evidence for role of serotonin in pathophysiology of schizophrenia, however serotonin receptors, mainly 5-HT_3 and 5-HT_6 are promising drug targets for alleviate cognitive and negative symptoms of the disease [35]. Agonists of 5-HT_{1A} receptor may reduce catalepsy induced by antipsychotic drugs [36].

3.4 GABAergic hypothesis

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system [37]. Proper functioning of GABAergic neurons is necessary for perception, memory, learning and cognition [38]. Imbalance between excitation and inhibition in the cerebral cortex is one of the main factors in the pathophysiology of schizophrenia. The cause of this may be disturbed activity of GABAergic neurons [39]. In patients with schizophrenia, we observe increased dopaminergic signaling, GABA may be useful in the treatment of schizophrenia because it has an inhibitory effect dopaminergic signaling [40]. Post mortem studies found the reduction of glutamic acid decarboxylase-67, which is needed to GABA synthesis. This lack of enzyme was found in brain parts linked with critical cognitive functions such as the dorsolateral prefrontal cortex [38]. In clinical studies, administration of GABA agonists decrease symptoms of schizophrenia [41].

3.5 Nicotinic receptors

It is known, that many people with schizophrenia smoke. Smoking rates in schizophrenia range as high as 70%, which is higher than in any other psychiatric disease[42]. Patients report that smoking helps them to relieve negative symptoms. Studies found that there is disturbed brain cholinergic transmission in patients with schizophrenia [43,44]. Those finding prompts research into the role of nicotinic receptors in pathogenesis of schizophrenia. Studies of nicotinic receptors found that α7 receptors are located in brain regions involved in cognition. Studying of α7 receptors with specific venomous toxins showed that α7 receptors are located in areas of the brain involved in cognition [45]. Nicotine or nicotinic agonists normalize many of the sensory processing deficits found in schizophrenia. These include electrophysiological measures of sensory processing such as P50 sensory gating, pre-pulse inhibition, and smooth pursuit eye movements [46]. In studies conducted on animals, nicotine improves performance on learning and memory tasks [47]. In patients with schizophrenia, nicotine improves performance on attention and working memory tasks, however, the duration of the effects is unknown [48]. Nicotinic receptors can be an attractive drug target for the treatment of schizophrenia.

4. Summary

There are numerous theories about pathogenesis of schizophrenia. However, neither of these theories fully explains the pathogenesis of this disease. Despite the fact that current concept and treatment are still based on the dopaminergic hypothesis of the disease, existing theories and each new theory, open up different ways for treating schizophrenia. Considering how severe the disease is, any new treatment method that gives hope for an effective, non-burdensome therapy is very important.

Schizophrenia is a complex multi-factor disease and according to the current knowledge it is not very probably that it can be treated using one single-target drug.

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