

Current targets and treatments of schizophrenia

Yutong Ding^{1,*}, Haoxiang Gao², Zhaoyi Liu³ and Xinyi Xu⁴

¹Wycombe Abbey School Changzhou, Nanjing, China

²Xi'an Tieyi High School, Xian, China

³Tsinghua University High School International-Chaoyang, Beijing, China

⁴Shanghai DTD Academy, Shanghai, China

*Corresponding author: 196061209@mail.sit.edu.cn

Abstract. With the improvement of the level of social and economic development, mental illness has received more and more attention and attention. Among them, schizophrenia, as a common mental illness, seriously impairs the mental activity and social function of patients, and its lifetime prevalence rate is about 1%, bringing a heavy social burden. Schizophrenia is a disease that involves a variety of symptoms, including cognitive, behavioral, and emotional, and its symptoms vary greatly from patient to patient, even at different stages of the disease in the same patient. At present, the specific pathogenesis of schizophrenia is still unclear, and it is generally believed that it is caused by structural and functional abnormalities of the central nervous system, which is the result of the interaction of genetic and environmental factors. Schizophrenia is a mental disorder disease, It can cause a person to be out of control in a number of ways and is a common and popular mental illness in the world, and recently, with advances and pioneering in the field of medicine, more and more neuroscientists and medical doctors are beginning to development into this field. This review systematically introduces several pathways related to schizophrenia disorders, anti-psychotic medications, and the GABA and schizophrenia. This review also introduces three generations Antipsychotics and further discusses role of GABA in the pathogenesis of schizophrenia.

Keywords: Schizophrenia, target, treatment.

1. Introduction

Schizophrenia is a mental disorder disease, It can cause a person to be out of control in a number of ways and is a common and popular mental illness in the world, and recently, with advances and pioneering in the field of medicine, more and more neuroscientists and medical doctors are beginning to development into this field. Dopamine is an important neurotransmitter, and dopaminergic pathways play two distinct but interrelated roles in the characterization of schizophrenia. The experiences of people with schizophrenia may seem peculiar and confusing to them. In an attempt to rationalize these seemingly uncontrollable and incoming experiences, they develop delusions. Antipsychotic medications alleviate positive symptoms by blocking D2 receptors, which reduces dopamine transmission and thus suppresses abnormal salience. Antipsychotics fall into two categories: typical drugs include chlorpromazine, fluphenazine, and haloperidol; atypical drugs include aripiprazole, clozapine, and lurasidone. Currently, antipsychotics specifically designed to eliminate problems at the D2 site are the most commonly prescribed medications.

Glutamate is a major excitatory amino acid neurotransmitter commonly found in the peripheral and central nervous systems. There are apparently at least two possible approaches to the treatment of schizophrenia that may target both the lack of NMDAR activity and the observed excess glutamate signaling. Indeed, pharmacologists have discovered or invented drugs that enhance NMDAR activity or reduce glutamate release. For the former, sarcosine, glycine, and D-serine are currently commonly used drugs. For the latter purpose, drugs such as MK0777, lamotrigine, and mGlu2/3 receptor agonists are used.

In addition to dopamine and glutamate, there is a third neurotransmitter that is thought to contribute to the symptoms of schizophrenia - serotonin. Dysregulation of the serotonergic pathway can also bring about changes that lead to psychosis. The serotonergic receptor responsible for this is the 5-

HT2A receptor. Discoveries have also been made in terms of drugs that interfere with the serotonergic signaling pathway. Recently, several new hypotheses have emerged, one of which relates to aminergic GPCRs other than dopaminergic and serotonergic receptors. Of these, noradrenergic and muscarinic receptors have received the most attention. Second, the first generation of antipsychotic drugs chlorpromazine, a traditional psychiatric drug, is a representative of the first generation of antipsychotic drugs, play a positive calming effect on psychiatric patients. However, it also antagonizes; other dopaminergic receptors in the normal pathway during treatment. This causes many negative effects on the patient. The second generation antipsychotic drug, Clozapine, is a much less negatively impacted alternative to first generation antipsychotics and is superior to other antipsychotics in reducing both positive and negative symptoms. Clozapine and other second-generation antipsychotics put patients at a lower risk of acquiring delayed dyskinesia than first-generation drugs. The third-generation antipsychotic drug, aripiprazole; is a dopamine D2 receptor partial agonist. Compared to clozapine, aripiprazole is better tolerated by patients and does not have any serious side effects.

Third, the study of GABA and schizophrenia mentions the GPCR; it is the largest group of membrane receptors in eukaryotes and plays a series of important roles in the human body, it is also known as the seven transmembrane receptor. When it binds to an external signal, the conformation of the GPCR changes, which triggers an interaction between the GPCR and the G protein onotropic receptor is a transmembrane protein that opens these ion channels when the ionotropic receptor binds to a ligand.

2. Possible neuronal pathways leading to symptoms of schizophrenia

Schizophrenia is a complicated disorder influenced by various factors. Over the past few decades, multiple neuronal pathways have been postulated that might lead to symptoms of schizophrenia.

2.1. Dopaminergic Hypothesis

Dopamine is a neurotransmitter with great significance. It is produced in both peripheral and central nervous systems and acts by interacting with G-protein coupled receptors (GPCRs). Various functions of dopamine include regulations of motor control, motivation, reward, etc [1]. Dopamine-related neuronal pathways are involved in the development of numerous neurological disorders, including the well-known Attention Deficit Hyperactivity Disorder (ADHD), Parkinson's disease and Huntington's disease [1]. While either hypodopaminergia in relation to the striatal region or direct degeneration of the striatum is observed in patients with the three listed diseases, it is the complete opposite case with schizophrenia.

Dopaminergic pathways play two distinct while interrelated roles in characterising schizophrenia. Hyperdopaminergia (i.e. excessive dopamine activity) in the mesolimbic pathway (which leads to the striatum), is thought to give rise to positive symptoms including both hallucination and delusion, which is assumed to be attributed to a process called aberrant salience of schizophrenia [3]. On the other hand, hypodopaminergia observed in the prefrontal cortex is considered to cause the negative symptoms of schizophrenia. There is also a causal linkage between the abnormality in the prefrontal cortex and the mesolimbic pathway, by which the former leads to the latter [2].

Salience represents the degree to which a stimulus is perceived as significant or relevant compared to others. It plays a notable role in assisting the brain to prioritise crucial information and the relevance between salience and dopamine is considerable. Salience is attributed by the salience network (SN), which functions as a moderator between two of the major stimuli-processing networks: central executive network (CEN) and default-mode network (DMN). The former is dedicated in processing external stimuli while the latter is for processing internal stimuli [4]. The incentive/motivational salience hypothesis states that dopamine is responsible for mediating the attribution of salience, especially in the mesolimbic pathway. Under normal circumstances, mediation is accomplished through stimulus-triggered transmission of dopamine. However, in the case of psychosis, salience is

made up by a dysregulated release of dopamine even without a stimulus, which renders the attribution uncontrollable [3]. As a consequence, aberrant salience arises, where excessive attention and inappropriate importance is assigned to certain stimuli or experiences. With the occurrence of aberrant salience, stimuli become misinterpreted. Consequently, experiences of schizophrenic individuals may appear peculiar, which baffle them [5]. In order to rationalise these seemingly uncontrollable and menacing experiences, delusions develop as a result. By contrast, it is a direct encounter of aberrant salience by individuals in the case of hallucinations. The subjects of misattribution of salience can either be internal representations or actions that are self-generated, which may account for visual or auditory hallucinations if those misappraised internal stimuli are interpreted as being generated externally [3,5]. In addition, the two symptoms can be connected as delusions may emerge to explain the existence of hallucinations.

Since aberrant salience caused by abnormal dopamine regulation is one of the underlying causes of psychosis, researchers have discovered antipsychotic drugs to treat schizophrenia by targeting the D2 receptor. Antipsychotic drugs relieve positive symptoms by blocking the D2 receptors, which lessen dopamine transmission and in turn dampen aberrant salience [3]. There are two categories of antipsychotics: typical ones include chlorpromazine, fluphenazine and haloperidol and atypical like aripiprazole, clozapine and lurasidone [6]. Currently, antipsychotic drugs that are dedicated in eliminating problems at the D2 site have been the most prevalent ones to be prescribed.

2.2. Glutamatergic Hypothesis

Although dopaminergic hypothesis has vastly promoted research on schizophrenia, some facets of this disorder are not explained. For example, the causes of negative and cognitive symptoms. Apart from this, it has been reported that antipsychotic drugs targeting D2 receptors are merely partly effective among schizophrenic patients. There must have been other influential factors [7]. To tackle these problems, researchers have proposed an alternative postulation--- glutamatergic hypothesis.

Glutamate is a major excitatory amino acid neurotransmitter commonly found in both the peripheral and the central nervous system. Glutamate can bind to an enormous number of receptors, which render it to be involved in more than 90% of excitatory signaling [8]. It functions by activating both ionotropic (ligand-gated ion channels) and metabotropic (GPCRs) receptors [9]. Some of its functions include regulation of learning, memory and sleep [8]. Through investigations, scientists have discovered that both positive and negative symptoms of schizophrenia, along with cognitive deficits, can all be a result of hypofunction of N-methyl-D-aspartate glutamate receptors (NMDAR) --- an ionotropic glutamate receptor, especially in the prefrontal cortex and hippocampus, leading to excessive glutamate transmission [9]. The exact mechanism is that, as glutamatergic pyramidal neurons become less γ -aminobutyric acid (GABA)-ergically inhibited due to hypofunction of NMDAR on fast-spiking GABAergic interneurons in the cortex, glutamate is released excessively, leading to symptoms of schizophrenia. This is called the 'disinhibition hypothesis' with regards to the reason for dysfunctional glutamate neurotransmission [7]. Furthermore, it has also been found that excessive glutamate release in the prefrontal cortex can actually account for downstream dopamine hyperactivity in the mesolimbic pathway [10].

Based on the glutamatergic hypothesis, it is clear that there are at least two possible approaches to treat schizophrenia, which may target both insufficient activity of NMDAR and superfluous glutamate signaling are observed. In fact, pharmacologists have already found or invented drugs that can either enhance the activation of NMDAR or attenuate glutamate release [7]. For the former approach, sarcosine, glycine and D-serine are commonly-used drugs nowadays. While to achieve the latter purpose, drugs like MK0777, lamotrigine and mGlu2/3 receptor agonist are used [11].

2.3. Serotonergic Hypothesis

Apart from dopamine and glutamate, there is a third neurotransmitter that is considered to be a contributing factor to symptoms of schizophrenia --- serotonin. Serotonin is a neurotransmitter with multiple functions, which include influence on learning, memory and reward on a mind level, as well

as regulating appetite, sleep and behaviour in terms of physiological control --- very similar to the role of dopamine. Serotonin is present in both the CNS and PNS and most of the serotonergic receptors are GPCRs [12]. The most common receptors being investigated that are involved in the serotonergic signalling pathway contributing to symptoms of schizophrenia are within the 5-hydroxytryptamine receptor (5HT receptor) family. These involve subtypes like 5-HT1A, 5-HT2A, and 5-HT2C receptors. The roles of the listed receptors in schizophrenia lie in their impact on mood and motivation-related behaviours, which are related to negative and cognitive symptoms [13].

Dysregulation within the serotonergic pathway can bring about changes that cause psychosis as well. The serotonergic receptor that is responsible for that is 5-HT2A receptor. It is hypothesised that excessive release of serotonin can result in psychosis in a chain reaction, in a causal sequence of: excessive serotonin release, hyperactivation of 5-HT2A receptors on glutamatergic neurons, excessively-released glutamate, hyperactivation of mesolimbic pathway, excessive dopamine release in the striatum, hyperdopaminergia, psychosis [10]. From this cascade, it is indicated that symptoms of a disorder may be mediated through interactions of several different factors. Scientists and researchers should not persist on only one possible pathway contributing to the disease. Instead, viewing the disease from various perspectives would provide alternative therapeutic targets, which better promotes the progression of research and drug development.

There are also discoveries made in terms of drugs that interfere with the serotonergic signaling pathway. For example, many atypical antipsychotics (e.g. olanzapine and risperidone) display efficacy against psychosis by acting on both D2 and 5-HT2A receptor. It has also been reported that atypical antipsychotics can have either direct or indirect effects on 5-HT1A receptors, which mostly improve negative symptoms and cognitive impairment [14].

2.4. Other Aminergic GPCRs Hypothesis

The three hypotheses listed above are the mainstream regarding the pathology of schizophrenia. Recently, there have emerged several more novel hypotheses, one of them is associated with aminergic GPCRs apart from dopaminergic and serotonergic receptors. These include adrenergic, muscarinic and histaminergic receptors. In particular, muscarinic M1, noradrenergic and histamine H1 receptors are currently the research hotspots [15]. Among these, noradrenergic and muscarinic receptors have received the most attention.

Noradrenergic receptors, mostly $\alpha 1$ and $\alpha 2$ adrenergic receptors, are acted on by the neurotransmitter noradrenalin. It is suggested that hyperfunction of noradrenalin system corresponds to positive symptoms, while hypofunction of the system gives rise to negative symptoms [16]. For muscarinic receptors, researchers have assumed their function to be alleviating dysfunction within both the dopaminergic and glutamatergic pathway [15].

2.5. GABAergic Hypothesis

Gamma-aminobutyric acid (GABA) interneurons play a critical role in the inhibitory neuronal pathway, particularly in the CNS. Various functions of GABA interneurons include regulating activity of the hippocampal and cortical regions, participating in neural oscillations related to cognitive functions, as well as integrating information.

Dysfunction in GABA transmission is responsible for cognitive deficits of schizophrenia. It has been reported from different animal and imaging studies that there is a conspicuous decline in levels of mRNA and proteins for the 67 kDa isoform of glutamic acid decarboxylase (GAD67), suggesting a reduction in the expression of GABA genes. GAD67 is an enzyme that synthesises GABA in the dorsal lateral prefrontal cortex (DLPFC), which has a remarkable role in memory and attention. In addition, the production of parvalbumin (PV) --- a calcium-binding protein, which is responsible for the release of GABA, has been observed to reduce in PV neurons. A combination of decline in the amount of both GAD67 and PV can lead to disinhibition by pyramidal neurons on excitatory cortical neurons, which in turn gives rise to altered neuronal oscillations in the cortex and hippocampus, as one role of GABAergic inhibitory pathways is to generate gamma oscillations. Diminished gamma

oscillations in the frontal cortex are responsible for deficits in the functioning of working and executive memory; while formation of episodic memories and processing of spatial information are regulated by gamma oscillations in the hippocampal region. In a nutshell, aberrant gamma oscillations are one of the contributing factors to the cognitive dysfunction in schizophrenia.

Two main therapeutic targets in GABAergic pathways are GABA_A and GABA_B receptors. GABA_A receptor is a ligand-gated channel for chloride ions affecting synaptic inhibition. One of the clinical drugs targeting this receptor is benzodiazepines (BZs). On the other hand, GABA_B receptors are GPCRs distributed extensively over the neuronal network. Their antagonists like CGP 36742 facilitate cognition by restoring neuronal oscillations and enhancing synaptic plasticity [17].

2.6. Abberant glial cells Hypothesis

Despite the pathways mentioned above, there is also an emerging hypothesis that states the possibility of glial progenitor cells contributing notably to the progression of schizophrenia. It is suggested that during embryogenesis, glial progenitor cells are impacted by immune activation of microglia, leading to defects in differentiation competence. Following that, maturation of macroglial cells including astrocytes and oligodendrocytes becomes influenced. Both abnormal glial progenitor cells and macroglial cells can contribute to symptoms, especially cognitive impairments, by impacting on transmission connectivity and neuromodulatory homeostasis respectively [18].

3. Three Generations of Antipsychotics

3.1. First-Generation Antipsychotics: Chlorpromazine

According to the dopaminergic hypothesis that was confirmed by the first-generation drugs, D2 receptors hyperstimulated might be the main factor for schizophrenia development. This means that unsuccessful dopaminergic transportation is a cause of schizophrenia [19]. First-generation antipsychotic medications primarily work by inhibiting the brain's dopamine D2 receptors. Known as conventional antipsychotics, chlorpromazine is a representative of the first-generation antipsychotics [19]. At the beginning, it was used as a medicine for reducing people's probability of getting in "shock" during the surgery, because it could reduce people's physical temperature [20]. It then became popular with psychiatry to use after the reports of psychiatrists Delay and Deniker shown that chlorpromazine had positive and sedative effect on psychopaths in 1952 [20].

A core function of chlorpromazine is blocking D2 receptors transmission of postsynaptic dopamine in the brain to reduce the positive symptoms of the schizophrenia patients [19]. It was immediately found after the discovery of Arvid Carlsson and Margit Lindqvist on mouse [21].

However, chlorpromazine cannot choose the location of a particular receptor for treatment. Therefore, it can also antagonize other dopaminergic receptors in the normal pathways during the treatment process. This brings many negative impact on drug users. This contains decreasingly cognitivity of the patients, parkinsonism and so on [19,20].

3.2. Second-Generation Antipsychotics: clozapine

Up to 30% of patients have treatment resistance, and the response to antipsychotics is frequently insufficient. There wasn't much that could be provided for such patients for a very long period. Meanwhile, since the numerous side effects of the first-generation antipsychotics, scientist explored for alternative medications with more efficient and fewer negative effects. In 1988, a typical research reported that clozapine brought significant improvements and fewer side effects in patients with treatment resistance [20]. Compared with the drugs before, the "atypical" second-generation antipsychotics such as like clozapine don't have extrapyramidal disturbances and can treat the schizophrenia positive symptoms with less side effects.

Furthermore, Clozapine antagonize has 5HT_{2A} receptors. It can be able to resistant slightly to the negative symptoms through changing dopaminergic tone, which is also an important factor to help patients avoid extrapyramidal side effects.

On the other hand, despite the risk of agranulocytosis, clozapine still has its superiority for treatment-resistant schizophrenia because it is better than other antipsychotics for reduction of both the positive and negative symptoms [22,23].

A clinical trial in Finland suggested that the frequency of side effects is much lower than other antipsychotic drugs, about 0.7%, and usually takes a mild form in [24].

Additionally, some meta-analyses supported that clozapine has lower probability to cause Parkinson's disease, because of the less use of antiparkinson drugs [24]. For Parkinson's disease, it also has more positive influence on efficiency and curative effect than placebo [25]. Other meta-analyses also shown that the second-generation antipsychotics like clozapine made patients get less tardive dyskinesia risk than first-generation drugs [26,27].

3.3. Third-Generation Antipsychotics: aripiprazole

The third-generation antipsychotics are dopamine D2 receptor partial agonist [28]. For the patients who can't tolerate clozapine, doctor had to find other drugs such as aripiprazole, brexpiprazole, cariprazine and lumateperone. They are able to treat positive symptoms of schizophrenia by stabilizing dopamine neurotransmission because their functional antagonism of excessive dopamine release reduced excessive striatal D2 receptor stimulation.

Among these mainstream antipsychotics, aripiprazole can activate D2 receptors as partial agonists, though it is not as well as dopamine [20]. It is also able to active DA receptors in regions like the prefrontal cortex with low concentration like [19]. With high concentration, aripiprazole is responsible for antagonizing DA receptors in the pathways to against psychosis. Compare with clozapine, aripiprazole is more tolerated for the patients and it doesn't have any severe side effects [29].

To sum up, the three generations of drugs above are all focus on antagonizing D2 receptors [21]. The treatment way is mitigate patients' positive symptoms to relieve secondary negative symptoms [30]. However, there is no any drugs discovered that can alleviate negative symptoms especially primary negative symptoms and cognitive symptoms directly [30].

4. GABA and schizophrenia

4.1. Role of GABA in the pathogenesis of schizophrenia

GPCRs are the largest membrane receptor group in eukaryotes which play array of important roles in human body [31]. GPCRs consist of a single polypeptide that is folded into a globular shape and embedded in a cell's plasma membrane. Based on its typical characteristic of structure, it also called seven-transmembrane receptors. GPCRs, an agent of signal, respond different types of extracellular stimuli, like hormones, nucleic acids, neurotransmitters, protein molecules, and so on [31]. The conformation of the GPCR will change after GPCR binds with the external signals, and this triggers the interactions between GPCR and G proteins.

The ionotropic receptor is the transmembrane protein often called as ligand-gated ion channels. Ionotropic receptors are coupled with some ion channels which can be opened when the ionotropic receptor binds with ligand [32].

GABA (γ -aminobutyric acid) is an important inhibitory neurotransmitter that can prevent chemical messages and decrease the stimulation pass between nerve cells [33]. GABA works in the opposite way with glutamate and it is generated by the reaction of decarboxylation of glutamate by the enzyme glutamic acid decarboxylase catalyzed. GABAA receptor and GABAB receptor are two kinds of receptors of GABA. GABAA receptor is a kind of ionotropic receptor that can control the Cl⁻ channel. When Cl⁻ ions flow inside the cell can lead to the membrane potential decrease and hyperpolarization. GABAB receptors belong to the C class GPCR [33]. GABAB receptor can as an ionotropic receptor can inhibits the release of other neurotransmitters. GABABRs have a high affinity for GABA, which are outside the synapse and widely spread in the brain. They can regulate neurodevelopment, neuronal network activity and synaptic plasticity.

The schizophrenia hypothesis about GABA can be supported by the reduction of GABA synthetase that found by autopsy studies. The disorder of GABA may lead to the balance between GABA and the imbalance of excitatory and inhibitory signals in the cerebral cortex [34]. Changed GABAergic synaptic transmission has been related to sleep abnormalities, anxiety, panic, impaired learning and memory. As a result, the memory circuits, learning ability and attention may be disrupted and weakened which are all typical cognitive symptoms of schizophrenia. In the hippocampus, gamma-band oscillations regulate network activity that promotes the encoding of spatial information and the formation of episodic memories. Some of the research shows that the GABAergic inhibitory circuits play an important role in the generation of gamma oscillations and synchrony [35].

4.2. Genetic study of GABA for schizophrenia

The changes in the expression of genes with known importance for developmental processes--like synaptogenesis, cellular migration, cell signaling, synaptic maintenance, immune regulation, glia, and mitochondrial function have been found in post-mortem tissue from patients with schizophrenia as well. The lack of GAD1 expression, the enzyme responsible for producing the majority of the GABA in the brain, can be usually found in many brain regions in the post-mortem tissue of patients with schizophrenia [36]. The deficit of GAD1 gene expression may cause molecular and behavioral dysfunction and GABAergic gene expression deficits.

RELN is important for the laminar organization and migration of the cortex and hippocampus. Moreover, RELN is discovered in plenty of GABAergic cells in multiple cortical layers shortly after birth. The reports of schizophrenic patients show that the expression of the RELN gene decreased [36]. Even just a little reduction of RELN might influence synaptic stability, synaptic integration during development and plasticity in adulthood. Moreover, RELN is expressed by GABAergic interneurons and plays a role to stabilize neurons and synapses. Some of the models show that the deficiency of RELN alone can cause the lessening of both GAD1 and BDNF in downstream. In conclusion, RELN is linked to the lack of GABAergic in schizophrenia [36].

The gene is located at 5q34-q35 that codes for GABR α 1. The GABR α 1 subunit can be found in most GABAA receptors [37]. Some of the studies have identified the expression of GABR α 1 mRNA decrease in the dorsolateral prefrontal cortex, lateral cerebella, and prefrontal cortex of patients with schizophrenia [37].

5. Conclusion

Patients with schizophrenia are often affected by the disease itself and long-term hospitalization drug treatment, and their social function and mental state are in a state of decline, manifested as lack of initiative, decreased will, emotional indifference, social isolation, aggression and violence. Traditional treatment is the use of antipsychotic drugs and other negative ways to control the condition, which cannot improve the patient's mental disability state, life ability, social function partial loss, resulting in a reduced quality of life. This review introduces several pathways related to schizophrenia disorders, anti-psychotic medications, and the GABA and schizophrenia.

Authors contributions

All the authors contributed equally and their names were listed in alphabetical order.

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