Schizophrenia: A Complex Mental Illness

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Introduction

The history of schizophrenia can be traced back to the documents that were written by Egyptians in 2000 B.C. Many signs and symptoms of schizophrenia were also described in ancient Greek, Roman, and Chinese manuscripts.

However, schizophrenia was initially described by the German psychiatrist Emil Kraepelin (1856) who used the term "dementia praecox" to describe a new nosological entity based on the descriptions of Ewald Hecker and Karl Ludwig Kahlbaum, respectively. Kraepelin attributed dementia praecox to organic changes in the brain and distinguished at least three clinical varieties of the disease: catatonia, hebephrenia, and paranoia. In 1911 Eugen Bleuler introduced the term "schizophrenia" published in "Dementia praecox Oder Gruppe der Schizophrenien" to describe the disorder previously known as dementia praecox. He thought that it was more appropriate to term as "schizophrenia" whose meaning is "split mind." Since its initial description, many researchers were dedicated to the study of schizophrenia. Kurt Schneider (1887–1967) provided a characterization of schizophrenic symptoms, using clinical observations without considering progression and prognosis of the disease [1]. Subsequently, Gabriel Langfeldt (1895–1983) pioneered the diagnostic criteria for schizophrenia by describing procedures that led to the identification of "schizophreniform psychosis" as a different disorder than "true schizophrenia" [2]. Although both mental disorders could be accompanied by delusions, hallucinations, disorganized speech, catatonic behavior, and social withdrawal, it is worth noting that the impairment level and duration of the disorder are different [3]. Examining the response to drug therapy, Timothy J. Crow classified schizophrenic patients in two types. The type I develop psychotic symptoms and exhibit a good response to neuroleptic agents, whereas type II is affected by negative symptoms and have a bad response to atypical antipsychotic agents [4]. Another prominent neuroscientist and psychiatrist is Dr. Nancy C. Andreasen, who carried out the first quantitative magnetic resonance study of schizophrenia and developed the first scale to measure schizophrenia symptoms. She also conducted a study using neuroimaging and genomic techniques. Peter Liddle studied the patterns of the cerebral blood flow associated with three syndromes of schizophrenia: psychomotor poverty, disorganization, and reality distortion. Psychomotor poverty syndrome is associated with decreased prefrontal dorsolateral cortex perfusion, while disorganization syndrome and

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distortion of reality are associated with increased perfusion of the right anterior part of the cingulate and medial temporal lobe, respectively [5].

In recent years, the human brain has been described as a complex network of structural and functional regions that are interconnected. Thus, brain function is not only attributable to the properties of certain regions or connections, but it arises from the organization in the brain network as a whole, the "human connectome." Therefore, the brain dysfunction could be a result of abnormal connections of neuronal networks. The altered connectivity could lead to a system integrity reduction as well as changes in the brain dynamics, producing a lower integration of information in the different brain systems [6]. In conclusion, schizophrenia is now thought as a disconnection disorder of functional brain networks [7].

Clinical Description

Schizophrenia is a mental illness characterized by psychosis, apathy, and social withdrawal in combination with the cognitive impairment that causes substantial changes in the patient's life. Among psychiatric disorders, schizophrenia is the most disabling disease that requires a large amount of health resources. New antipsychotic treatments were developed so that schizophrenics can lead a reasonably normal life. The estimated annual incidence is 0.2–0.4 per 1000, and the frequency of occurrence is similar in both sexes, although it is more benign and tends to appear later in women [8].

Schizophrenia is a complex disease characterized by three clinical symptoms: positive or psychotic symptoms, negative symptoms, and cognitive impairments. Firstly, a prodromal or clinical high-risk syndrome has been described in which a young person manifests attenuated forms of delusions and hallucinations, associated with a high risk for conversion to full psychosis within a few years. Among the individuals who convert, approximately 80% of the diagnostic outcomes are found in schizophrenia spectrum, and the remaining 20% are related to mood disorders and atypical forms of psychosis [9, 10]. It should be noted that positive symptoms occur as outbreaks throughout the patient's lifetime, while negative symptoms are described as a reduced basic behavior in the course of the pathology. Cognitive impairments are described as attentional disturbance and alterations in concentration, memory, and operational function alterations. Negative symptoms and cognitive disorders impact the patient's social life since the patients may be exposed to alcoholism, substance abuse, or post-traumatic stress disorder resulting in a high suicide rate (calculated at 5%) and accident risks [8].

An experimental approach has been applied to study the most relevant symptoms of schizophrenia. Delusional perception is studied as representative of positive symptoms, while affective flattening is used to examine negative symptoms. Cognitive impairments are studied by impairment of working memory and acquisition deficits. All these researches lead to the implication of glutamatergic neurotransmission in the nucleus accumbens septi (NAS), another brain structure involved in schizophrenia [11].

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) is an American Psychiatric Association publication that describes the following schizophrenia subtypes: paranoid, disorganized, catatonic, undifferentiated, and residual type. However, *DSM-V* (2013) modified the method of classification since it decided to joint all these categories in a single heading: schizophrenia. Therefore, an individual has to manifest at least one of the following symptoms—delusions, hallucinations, and disorganized speech—to be diagnosed as a schizophrenic patient. Schizophrenia is considered a spectrum disorder represented by symptoms that occur in a continuum and certain characteristics shared across the spectrum in which these symptoms are manifested in markedly different forms and degrees [12].

Etiology

Schizophrenia is a neurodevelopmental disorder which is the result of multiple factor interactions such as viral illnesses during pregnancy,

environmental agents, immunological dysfunction, or obstetric complications. The neurodevelopmental theory states that patients acquire schizophrenia from an immature brain injury that results in abnormal neuronal growth and damage. The subsequent psychotic outbreaks can originate a neurotoxic phenomenon, so the disease is now considered both neurodegenerative and neurodevelopmental disorders [13].

Then schizophrenia may be produced by prenatal factors which are pathological situations that occur in the second trimester of pregnancy, a crucial period of maturation and differentiation of the primitive CNS. In addition, perinatal factors that are obstetric complications during the birth also predispose to schizophrenia**.** Social factor can lead to schizophrenia in vulnerable patients, who have a genetic basis for disease development, for instance, patients with a family history of psychosis and urban residence as a social factor [14, 15].

The gene loci 22q11–13, 6 p, 13q, and 1q21–22 are linked to different neurological functions, i.e., genes that regulate the biological system at the molecular level [16]; a single gene does not encode for schizophrenia, but many genes would be involved in forming a chromosomal basis of risk for developing schizophrenia [17].

Several lines of evidence have confirmed that catechol-o-methyl transferase allelic variants (an enzyme which is involved in the metabolic degradation of cathecholamines, especially dopamine in the prefrontal cortex) influence significantly abnormal psychological performance of schizophrenic patients [18]. The breakthrough of specific synaptic dysfunctions in schizophrenia drives the attention to genes that encode synaptic proteins. DTNBP1 encodes dysbindin-1 protein, which is located within chromosome 6p22.3. Dysbindin-1 is a 40–50 kDa protein that binds to α- and β-dystrobrevin, both components of the dystrophin glycoprotein complex. Dysbindin-1 is located in postsynaptic densities in certain brain areas; thus any variation in DTNBP1 might confer risk of schizophrenia due to effects on postsynaptic structure and function [19].

Neurotransmission systems like GABAergic, glutamatergic, and dopaminergic are implicated in the schizophrenia, and their synaptic receptors are associated with G protein and regulated by RGS proteins, so that an alteration in RGS4 gene would be producing a significant decrease in cortical RGS protein level in schizophrenics [12]. The World Health Organization (WHO) has studied the incidence of schizophrenia in several countries. The stress produced by the impossibility of accessing to a mental health system is a problem that affects at about 50% of schizophrenics.

In general, schizophrenics do not receive an adequate treatment because they are less disposed to seek medical assistance or cannot afford their treatments (therapy drugs, psychotherapy, etc.) [17]. In terms of neurodevelopment, schizophrenia is considered as the result of a complex interaction between genes that contribute to the risk and genes that offer protection, added to environmental factors that are expressed in the course of the development. Therefore, the environmental factor can modify genetic basis; thus the interaction between genes and environment could be involved in the genesis of psychosis [20].

Schizophrenia and other major psychiatric disorders are also associated with abnormalities in multiple epigenetic mechanisms, resulting in altered gene expression during development and adulthood [21]. The epigenetic mechanisms are modifications that occur in the genetic material that do not change the nucleotide sequence but instead may cause modifications in DNA conformation. Thus, epigenetic deregulation of the genome and direct CNS injury are probably the main mechanisms to mediate prenatal environmental effects, whereas postnatal risk factors (e.g., stress, cannabis use) may also affect risk via use-based potentiation of vulnerable CNS pathways implicated in schizophrenia [22].

Three epigenetic modifications, DNA methylation, histone modification, and regulation by noncoding RNA, have been described, but the most used epigenetic mechanism in animal models of schizophrenia is DNA methylation. In mammalian cells, DNA methylation occurs in the 5′ position of the cytosine residues that precedes a guanosine in the DNA sequence, called the CpG dinucleotide which are mainly present of the gene

promoter; in general CpG islands are hypo- or unmethylated in normal cells and allow for the active gene transcription. DNA methylation is a crucial step to gene expression or gene silencing preventing or promoting the recruitment of regulatory proteins, such as nuclear co-regulators and transcriptional factors. L-Methionine (MET) administration to patients produces the worsening of psychotic symptoms, which were reproduced in MET-induced mice [23]. L-Methionine supplementation in rats induces epigenetic variations including reelin promoter hypermethylation in offspring [24]. Schizophrenia has also been associated with a global increase in microRNAs (miRNAs) biogenesis and expression in the cerebral cortex [25].

CNS Areas and Neurotransmission Systems Involved in Schizophrenia

Anatomical and functional modifications were studied by magnetic resonance imaging performed for patients at the onset and chronic stage of the disease. The results indicated that there was no correlation since these modifications have been occurring in different brain regions. The antipsychotic treatment produces a clinical improvement, but the functional modifications are maintained throughout the patient's lifetime.

A recent research has focused on changes in neuronal connectivity and microcircuits of cortical layers that show an increase in clustered neuronal groups and a decrease in the density of neurophil and dendritic spines in the pyramidal neurons of the prefrontal cortex [26]. The prefrontal cortex is a cerebral region involved in the executive function's performance, being deregulated in schizophrenia [27, 28]. For this reason, working memory tests and imaging studies in simultaneous was used to demonstrate that schizophrenics were unable to complete these tasks, whose results were interpreted as a deficit in the prefrontal cortical activity or hypofrontality [29]. Dopaminergic transmission in the prefrontal cortex is mainly mediated by D1 receptors; thus D1 dysfunction has been linked to cognitive impairment and negative symptom of schizophrenia [30]. Additional researches have proved that prefrontal cortex remains hyperactive, not resulting in a possible further activated [31]. The hippocampus is another area that remains hyperactive [32–34], and this hippocampal hyperactivity has perfectly correlated with psychosis [35]. Therefore, the psychotic features of schizophrenia can be driven by abnormally heightened hippocampal activity.

In fact, basic studies have reported that the activated hippocampus leads to a hyperdopaminergic state [36]. Initial evidence for GABAergic hyppocampal abnormalities came from studies that showed a decrease in the number of GABAergic interneuron in schizophrenia. Furthermore, it has been disclosed a reduction in gene and protein expression of somatostatin-positive and parvalbumin-positive interneurons involving to GABAergic system [37].

The basal ganglia associated with the prefrontal cortex are implicated in the motivation, emotion, and reward. The striatum is part of a motor circuit, its association with premotor cortex, motor cortex and other brain areas is involved in regulation of the motor and sensitive information. The afferent nerve fibers that come from the prefrontal cortex, the amygdala, the thalamus, the ventral tegmental area, and the substance nigra pars compacta arrive at the basal ganglia, whereas the efferent nerve fibers go to Globus pallidus and substantia nigra pars reticulata which are GABAergic structures and to the glutamatergic subthalamic nucleus that projects to the thalamus [38].

The cerebellar system is also implicated in schizophrenia because it is behaving like an adaptive regulatory system of the cerebral cortex and the brainstem. Normal subjects and patients have been subjected to memory tasks and positron-emission tomography (PET) studies that provide an accurate description of a memory circuit, which is made up to the prefrontal cortex, thalamus and cerebellum. In addition, these studies have proved that the brain areas involved in the circuit remain inactive in the schizophrenic patients [39]. The thalamus receives inputs of the reticular system, cortical areas, and the amygdala. Thus, impulses generated in the amygdala toward the frontal cortex come from the ascending pathway which is the inferior thalamic peduncle. The hyperdopaminergic state inhibits

to the thalamus, which leads to an increase in stimuli reaching the cerebral cortex producing the characteristic symptoms of schizophrenia [40]. Daniel R. Weinberger described a feedback of the cortico-subcortical circuit, highlighting the importance of dopaminergic activity of mesolimbic and mesocortical pathways [41].

The most accepted theory has been the dopamine hypothesis, although supporting evidence was indirect such as psychotic effect produced by dopaminergic agonists [42]. Over time, dopaminergic theory has been modified based on experimental tests that provide new data on the molecular mechanisms involved in the disease. Firstly, the dopamine receptor was involved; this idea arose from the discovery that antipsychotic drugs act as dopamine receptor antagonists [43] demonstrating the requirement for a dopamine receptor blockade to treat the disease [44, 45]. In a subsequent revised version, the main idea was that schizophrenia would be associated with a deregulation of dopamine transmission since it would be observed as a hyperfunction of the mesolimbic dopaminergic subcortical projections leading to D2 receptor hyperstimulation with the occurrence of positive symptoms. Then, coexistence of hyperdopaminergic and hypodopaminergic states due to an alteration of modulation of dopamine activity has been raised [46, 47]. This modulation depends on dopamine receptor interactions due to the existence of homeostatic regulatory mechanisms, which are involved in decreasing or increasing the number of dopamine receptors depending on the dopamine levels. Thus, an excess of dopamine concentrations into the synaptic cleft produces a dopamine receptor reduction, but the opposite occurs when dopamine concentrations are decreased. In normal conditions, certain stimuli such as stress produce a phasic dopamine release and a rapid uptake without the presence of the homeostatic mechanism described. However, during the rest the dopamine is released into the synaptic cleft in a tonic and sustained manner, activating the homeostatic mechanism and regulating dopamine receptor density. This tonic dopamine release would be maintained by cerebral cortex activity through cortico-subcortical glutamatergic projections, which lead to a suitable dopaminergic tone [47]. Subcortical dopamine deregulation observed in schizophrenia could be secondary to a prefrontal cortex failure [47–49]. Thus, Arvid Carlsson has described a model in which the prefrontal cortex modulates the midbrain activity by an activating pathway, which consists of glutamatergic projections toward dopamine neurons and the other inhibitory pathway constituted by glutamatergic projections toward GABAergic interneurons [43]. According to Grace's model, in schizophrenia exists a cortico-subcortical hypoglutamatergia with the diminish of tonic dopamine release resulting in a dopamine decrease in the synaptic cleft, and then a homeostatic mechanism of dopaminergic hypersensitivity is activated, producing the postsynaptic dopaminergic hyperactivity in response to a phasic dopaminergic activity [47].

Recently, Oliver Howes and Shitij Kapur (2009) have reported the version III of the dopamine hypothesis whose name is "the final common pathway" where the authors have hypothesized that multiple "hits" interact to result in dopamine deregulation at the presynaptic level. In addition, the dopamine deregulation is linked to "psychosis" rather than schizophrenia, and perhaps in the course of time, it will be about "psychosis proneness" [17]. Another neurotransmitter system involved has been the serotoninergic system, since hyperfunction of serotonin 5-HT2A receptors in schizophrenia has been reduced by the blockade of clozapine, an atypical antipsychotic agent which is effective to control negative symptoms [50].

Several neurochemical studies have demonstrated the existence of abnormalities in the cerebral glutamatergic transmission of schizophrenic patients, ranging from the reduction of glutamate levels in the cerebral cortex to modifications in NMDA, AMPA, and kainate receptor subunits located in the hippocampus, the medial temporal lobe, and the thalamocortical circuits. The hypothesis that glutamatergic system hyperactivity occurs in schizophrenia arises from the observation of psychotic states induced by NMDA antagonists such as phencyclidine (PCP) or ketamine. Thus, NMDA receptor inhibition predominately decreases the activity of putative GABA neurons but, at a delayed rate, increases the firing rate of the majority of pyramidal neurons.

NMDA receptors preferentially drive the activity of cortical inhibitory interneurons suggesting that NMDA receptor inhibition causes cortical excitation by disinhibition of pyramidal neurons. These findings support the hypothesis of NMDA receptor hypofunction, which has been implicated in the pathophysiology of schizophrenia, diminishing the inhibitory control of prefrontal cortex output neurons [51]. Dopamine D2 receptors can regulate glutamate release from cortico-limbic and cortical-striatal terminals due to their presynaptic location in these terminals. D2 antagonist can modulate the fine tune in the release of glutamate from key neurons in the cortical and limbic regions [52].

Several lines of evidence suggest that brain cholinergic neurons play an important role in schizophrenia, so modulation of cholinergic activity may represent a therapeutic benefit [53]. In particular, cholinergic neurotransmission has been involved in cognitive deficits associated with schizophrenia [54]. Several researches have shown that muscarinic acetylcholine receptor density is reduced in the prefrontal cortex, hippocampus, and basal ganglia [55]. Muscarinic antagonists produce psychotomimetic effects in schizophrenic patients, supporting the idea that the cholinergic system would be involved in the genesis of psychosis [56]. M1 acetylcholine receptors have an important role in regulating brain regions that are altered in schizophrenia. In this regard a single-nucleotide polymorphism in the M1 acetylcholine gene has been associated with prefrontal cortical dysfunction in schizophrenia. M1 acetylcholine receptors possess an allosteric site that can be activated by selective agonists producing certain cognitive benefits in schizophrenia [57]. AC42 is a small molecule that behaves as a selective agonist of the M1 receptor, since it binds to the ectopic/allosteric site and has no affinity for other muscarinic receptor subtypes. The alkaloid brucine is other example of M1 allosteric modulators. The M2 acetylcholine receptor is another attractive target since it has been involved in neuronal plasticity and cognitive process, but new agonist development is limited because the M2 receptor takes part both in central as in cardiac effects [58]. M4 acetylcholine presynaptic receptors are found in midbrain cholinergic neurons, which originate in the laterodorsal and the subpeduncular tegmental nucleus as well as pedunculepontine tegmental nuclei. Thus, they control acetylcholine release in the dopaminergic afferents that project to the nucleus accumbens controlling the hyperactivity of the dopaminergic mesolimbic pathway [53]. Acethylcholinesterase inhibitors produce an increase in endogenous acetylcholine, which can interact with muscarinic and nicotinic receptors. Canadian families of schizophrenic patients have shown that the M5 receptor gene in combination with α7 nicotinic acetylcholine receptor gene located in the cromosoma15q13 would be related to schizophrenia [59]. Single-nucleotide polymorphism of α7 nicotinic acetylcholine receptor gene [60] has been disclosed. The α7 nicotinic acetylcholine receptor is reduced in the hippocampus and dorsolateral prefrontal cortex in schizophrenic patients [61]. This reduction is relevant since α7 nicotinic acetylcholine receptor is densely expressed in parvalbumin GABAergic interneurons where it provides rapid cholinergic excitatory transmission. This suggests that any alteration in glutamate and acetylcholine transmission could lead to modifications in the effectiveness of the GABAergic neurotransmission [62].

Regarding neuropeptide systems, cholecystokinin (CCK) reduction is observed in the temporal cortex, the hippocampus, and the amygdala of schizophrenic brain. The somatostatin reduction in the hippocampus and substance P and vasoactive intestinal peptide (VIP) reduction in the amygdala and hippocampus of patients' brain are observed. It should be noted that CCK behaves as a co-transmitter that inhibits the dopamine release; thus in schizophrenia a reduced CCK level produces an increase in dopamine activity. Opioid peptides are related to the development of schizophrenia symptoms, such as auditory hallucinations, but the administration of opioid agonist or antagonist does not produce any clinical outcome [63].

Finally, neurotensin is found in rich areas of neuronal bodies and terminals on the dopaminergic system where neurotensin exerts the regulation of dopamine activity [64]. The effects of neurotensin occur when the peptide binds to receptors termed NTR1, NTR2, and NTR3; the NTR1 and NTR2 are receptors coupled to G

proteins and participate in the regulation of Na^+, K^+-ATPase, an enzyme involved in neurotransmission. However, neurotensin inhibitory effect on Na^+, K^+-ATPase has not been recorded in an animal model of schizophrenia, which is obtained by the administration of a nitric oxide synthase inhibitor during the postnatal period [65, 66].

It is known that dopamine receptors also belong to G-protein-coupled receptor (GPCR) family. These receptors can exist as monomers, dimmers, or higher-order oligomers which conform assembles with their peers (D1/D2 or D2/D3) and other GPCRs, ion channel receptors, tyrosine kinases receptors, scaffolding proteins, and transporters [67]. Neurotensin can reduce the affinity of dopamine D2 receptor (D2R) agonist binding sites, which correlated with its ability to counteract the DA agonist-induced inhibition of striatal DA and GABA release and to induce neuroleptic actions. NT produces via an antagonistic allosteric NTR1-D2R receptor-receptor interaction, a reduction in the D2R agonist-induced activation of Gi/o proteins, and β-arrestin-mediated internalization due to a biased modulation of the dopamine D2 receptor protomer [68]. These results have a therapeutic relevance for treatment of schizophrenia since they have indicated that NTR1 protomer in the D2R-NTR1 heteroreceptor complex can reduce D2R protomer signaling. Therefore, the development of NTR1 agonists and positive allosteric modulators would be considered as a relevant strategy for the design of new therapeutic drugs [69].

Schizophrenia Treatments

Drug treatments for schizophrenia are based on the dopamine hypothesis concerning the symptoms of this disorder. Typical antipsychotic agents induce a nonselective dopamine D2 receptor blockade which produces side effects such as involuntary movements known as extrapyramidal effects and the increase of prolactin levels [70]. Atypical antipsychotic agents are better tolerable than typical antipsychotic agents, especially in relation to extrapyramidal side effects [71]. Iloperidone is a new atypical antipsychotic that received marketing approval for the acute treatment of schizophrenia [72]. Lurasidone is an antagonist of dopamine D2 receptor and serotonin 5-HT2A and 5-HT7 receptors and is a partial agonist of serotonin 5-HT1A receptor, reducing the risk of relapse after a long-term treatment [73]. Both aripiprazole and brexpiprazole are partial agonists of 5HT1A, D2, and D3 receptor and an antagonist of 5HT2A that produces a lower risk of extrapyramidal effects [74]. Paliperidone palmitate is a long-acting injection that can be used as an acute treatment even in an outpatient setting [75]. Asenapine is a new sublingual atypical antipsychotic drug that behaves as an antagonist at several dopamine, serotonin (5HT2A, 5HT2B, 5HT2C, 5HT6, and 5HT7), and alpha adrenergic receptors (α1 and α2). Asenapine has no activity at muscarinic receptors in the therapeutic dose range. Hence, it does not cause any anticholinergic adverse effects and metabolic syndrome but may produce weight gain and sedation due to histamine H1 receptor antagonist [76].

D3 dopamine receptor (D3R) is another pharmacological target that appears to play a role in the schizophrenia; hence, cariprazine is a partial D3R agonist that produces antipsychotic-like effects in preclinical animal models. Cariprazine was approved in 2015 by the US Food and Drug Administration for the treatment of schizophrenia. Cariprazine may also reduce the risk of dopamine-related adverse effects further due to its partial agonist effect on 5HT1A, which may reduce extrapyramidal symptoms and improve mood and cognition [71]. ALKS 3831 is a fixed-dose combination of samidorphan, a mu-opioid receptor antagonist, and the atypical antipsychotic drug olanzapine. The combination treatment uses the action of samidorphan to reduce the weight gain and metabolic adverse events associated with olanzapine while maintaining olanzapine's antipsychotic efficacy. MIN-101 is a first-in-class 5-HT2A and sigma-2 receptor antagonist in the same molecule. The blockade of serotonin 5-HT2A receptors reduces hallucinations, delusions, and movement disorders associated with schizophrenia. Moreover, sigma-2 receptor antagonism modulates dopamine transmission and improves the negative symptom control [77]. Recently, the N-methyl-D-aspartate (NMDA) receptor hypothesis of schizophrenia

has been validated in animal models and patients [71]. Phencyclidine (PCP) animal model of schizophrenia has been useful to study the disruption of the dopamine D4 receptor interaction in the prefrontal cortex where clozapine restored D4 receptor regulation of NMDA receptor in this animal model. New antipsychotic agents that are mGluR2/3 receptor activity modulators have been developed by schizophrenia treatment at an early stage. However, they failed to demonstrate clinical efficacy in this condition, and some of them produced centrally mediated side effects, limiting their routine use [78]. Lately, new generations of glutamate-enhancing compounds that allosterically enhance the functionality of mGluR2 have been discovered, and their effects are being evaluated [79].

The heavy users of cannabis as well as individuals who abuse with highly potent preparations of cannabis, which contain roughly 15% delta-9-tetrahydrocannabinol (THC), have an increased risk of schizophrenia. Differently, cannabidiol is a negative allosteric modulator of the cannabinoid 1 (CB1) receptor that reduces the psychogenic effect of THC and may possess antipsychotic properties [71].

Conclusion

The study of anatomical, functional, and neurotransmission system modifications has been extensively performed to achieve a better understanding of schizophrenia and the possibility of developing new treatments.

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Conflict of Interest There is no known conflict of interest associated with this publication.

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