Schizophrenia: Current Hypotheses, Treatments, and Future Directions

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Abstract

Schizophrenia is a psychological disorder that predominantly manifests in men during their early 20s, a few years later in women, and affects one percent of the world population. The disorder is characterized by the expression of positive and negative symptoms as well as cognitive impairments. Positive symptoms include hallucinations and delusions, while negative symptoms include social withdrawal and loss of motivation. Pharmacological treatment of the disorder has been centered around antipsychotics, but results have been inconsistent and typically ineffective for negative symptoms. Combination therapy with forms of psychosocial interventions have been effective in some patients. Early research focused on alterations to dopaminergic transmission which led to the development of the dopamine hypothesis. More recently, the N-methyl D-aspartic acid (NMDA) receptor hypofunction hypothesis was developed, implicating a more complicated underlying etiology of the schizophrenic symptoms. Together, these hypotheses provide information on the molecular underpinnings of schizophrenia, but our understanding is still incomplete. The interplay between dopamine and NMDA receptor transmission has become the focus of current research. With the continuous improvement of imaging technology, a deeper understanding of the origins of schizophrenia may be on the horizon. This review will discuss current schizophrenia hypotheses and address gaps in the research field. Finally, potential directions will be proposed to attempt to fill those gaps.
Introduction

Schizophrenia is commonly characterized psychiatric disorder of the central nervous system and has been ranked as one of the top ten contributors to the global burden of disease by the World Health Organization (American Psychiatric Association, 2013). However, schizophrenia has begun to be viewed as a syndrome, or a collection of signs and symptoms, with the underlying cause remaining elusive. Impairment of social and occupational functioning as well as psychosis, either chronic or recurrent, occurs in schizophrenia and these typically manifest during early to mid 20’s in males with a somewhat later onset in females (Fischer & Buchanan, 2020). Schizophrenia is characterized by cognitive impairment along with positive and negative symptoms which are being targeted by current therapies. Positive symptoms include hallucinations, delusions, and sporadic thoughts and behavior (Carpenter et al., 1974; Fischer & Buchanan, 2020). Negative symptoms include social withdrawal, reduced energy, and apathy (Strauss et al., 2013). Patients can present with a combination of both positive and negative symptoms, causing individualized treatment to be difficult. The current understanding of the predispositions for schizophrenia is far from adequate but research is being done into genetic and environmental factors that influence the onset and severity of the disorder.

Pharmacological interventions aimed to treat schizophrenia have shown some efficacy with regards to positive symptoms but have been unable to address negative symptoms and cognitive impairment (Fischer & Buchanan, 2020). Antipsychotic agents are typically first-line medication for patients with schizophrenia though they can produce their own side effects. Combining antipsychotics with psychosocial interventions has shown promise but this
improvement is not universal (Stroup & Marder, 2019). About one third of schizophrenic patients fall into the category of treatment-resistant and do not respond to first generation antipsychotics (Mortimer et al., 2010). These patients are often prescribed second generation antipsychotics like clozapine (Stroup & Marder, 2019) which has proven to be the only antipsychotic more effective at treating both positive and negative symptoms than first generation antipsychotics (Leucht et al., 2003; Stone et al., 2007). The need for a more effective treatment is apparent, especially when observing the rate of suicide within schizophrenic populations. Close to five percent of patients diagnosed with schizophrenia commit suicide (Hor & Taylor, 2010) and around ten percent of successful suicides occur in schizophrenic patients (Arsenault-Lapierre et al., 2004; Suominen et al., 2002).

Developing a more efficacious treatment requires an understanding of the molecular basis of the disorder and is what schizophrenia research has focused on since Philip Seeman’s work during the 1970’s (Philip Seeman, 1987; Philip Seeman & Lee, 1975). Some major revelations from the half century of research into schizophrenia include the development of the N-methyl D-aspartic acid (NMDA) receptor hypofunction hypothesis (Stone et al., 2007), the dopamine hypothesis (Philip Seeman, 1987), and the implications parvalbumin positive (PV⁺), fast-spiking interneurons (FSIs) appear to have in the psychopathology and symptoms (Perry et al., 1979; Bird, 1985; Nakazawa et al., 2012). As research moves forward and underlying mechanisms continue to be parsed apart, this opens doors for the development of more targeted treatments and therapy. Current medications work to temporarily alleviate the symptoms but come with other adverse side effects and fail to treat the disease itself. This review will discuss
what is currently known and still unknown about the pathological development and treatment of schizophrenia.

**NMDAR Implications in Schizophrenia**

Arguably the most extensively studied mechanism involved in schizophrenia is the glutamate hypothesis involving NMDA receptors. With much of the early focus of deciphering the molecular basis of schizophrenia falling on the DA D2 receptor, the emergence of a different explanation focusing on NMDA receptor function has proven promising. The NMDA receptor is one of three neuronal ionotropic glutamate receptors alongside the AMPA and kainate receptors (Coyle, 2006). It has been shown to be critical in synaptic plasticity and helps aide the AMPA receptor in excitatory postsynaptic current (EPSC) generation (Coyle, 2006). The NMDA receptor channel is blocked by a Mg$^{2+}$ ion at resting membrane potential which is removed when the cell becomes depolarized. In addition to the primary glutamate binding site, a second ligand binding site termed the glycine modulatory site (GMS) must have a ligand bound for glutamate to correctly open the channel (Berger et al., 1998). Following the opening of the NMDA receptor channel, an influx of Ca$^{2+}$ leads to the effects modulated by NMDA receptor activation. These include gene expression alterations (Hong et al., 2004) and persistent upregulation of AMPA receptor function during the induction of long-term potentiation (LTP), a molecular correlate of learning and memory (Malenka et al, 2003). Excessive activation of these NMDA receptors can lead to an increase in oxidative stress and excitotoxic effects on neurons, factors that need to be taken into account when developing potential therapeutics (Coyle, 2006).
There have been several separate areas of research that have given the NMDAR hypofunction hypothesis support: NMDA receptor antagonists, pharmacological interventions targeting NMDA receptor hypofunction in schizophrenic patients, postmortem and brain imaging studies (Coyle, 2006), and genetic studies (O. Howes et al., 2015). Coyle (2006) argues that these areas of research have identified glutamate/NMDAR hypofunction as a more persuasive argument for the molecular basis of schizophrenic symptoms than dopamine. Javitt and Zukin were the first to propose the idea that psychomimetic effects seen in phencyclidine (PCP) use were due to an NMDA receptor blockade in 1991. This hypothesis received considerable support from Krystal et al. (1994) when they showed that a steady low dose of ketamine in normal volunteers induced the negative symptoms and cognitive deficiencies similar to those seen in schizophrenic patients as well as limited positive symptoms like illusions. Ketamine and other dissociative anesthetics like MK-801 are non-competitive NMDA antagonists that bind to a site within the channel. Building upon the findings of Krystal et al., (1994), Newcomer et al. (1999) were able to show that the type of memory impaired in schizophrenia, declarative memory, was sensitive to low dose ketamine infusions. Taken together, these studies suggest that ketamine replicates negative symptoms of schizophrenia more accurately than positive symptoms.

**Dopamine Hypothesis of Schizophrenia**

As mentioned, schizophrenia is a complicated, multifaceted disease and is not the result of a singular mechanism. The next hypothesis discussed here involves another well-known
neurotransmitter, dopamine (DA). DA and dopaminergic transmission were the main focus of schizophrenia research for the latter half of the 20th century. The interest was due to the success seen in treating schizophrenic patients with antipsychotics, DA D2 receptor antagonists (Philip Seeman & Lee, 1975). This resulted in the first hypothesis positing a hyperactive DA transmission as the mechanism behind the cognitive deficits seen with schizophrenia (Carlsson & Lindqvist, 1963; Laurelle et al., 2003). Initial research focused on the nucleus accumbens (NAc) and striatum, as this is where the D2 receptor localizes. More recently it has been found that many negative and cognitive symptoms do not respond to antipsychotic treatment. Additionally, DA D1 receptor transmission reduction within the prefrontal cortex (PFC) may be a contributing factor to the observed symptoms (Knable & Weinberger, 1997). These observations along with those of Davis et al., 1991 and Weinberger, 1987 led to the formation of a new hypothesis implicating reduced PFC DA D1 receptor transmission in the negative symptoms and cognitive deficits in schizophrenic individuals (Laurelle et al., 2003).

Dopamine D2 Receptor Hyperstimulation:

In the 1990’s, numerous imaging studies have provided data in support of the DA D2 hyperstimulation were performed. Radioactive tracers were used which compete with neuroreceptor binding sites of endogenous neurotransmitter (NT) to indirectly measure NT levels. Schizophrenia doesn’t alter the D2 affinity for DA, allowing these measures to approximate DA release (Laruelle, 2000b). This approach is not entirely accurate as mechanisms like agonist induced internalization of receptors is not accounted for (Laruelle, 2000a), but still provided convincing evidence for the abnormal D2 activation levels in
schizophrenic patients. Amphetamine-induced DA release was another measure reported in many studies to be increased in schizophrenic patients when compared to controls (Abi-Dargham et al., 1998; Breier et al., 1997; Laruelle et al., 1996, 1999). Laurelle et al., (2003) reported a greater than two-fold response to the amphetamine challenge, which is consistent with increased DA release. Importantly, positive symptoms were exacerbated in schizophrenic patients following amphetamine challenge and this increase was seen to dissipate after a few hours. The increased D2 activation that follows amphetamine challenge mirrors the increase in positive symptoms, strengthening the association between hyperactivation of DA D2 receptors and schizophrenic pathology (Laruelle, 2000a).

Major criticisms of the aforementioned research emerged. First, amphetamine and other drugs used to modulate DA release, like reserpine, target other brain monoamines leading to the potential of confounding results (Davis et al., 1991). Secondly, it was questioned whether the stress from the experimental protocol was the true cause of the elevation in DA release since stress has been shown to increase DA release (Deutch et al., 1990). To address this, Parsey et al., 2001 examined amphetamine-induced DA release in nonpsychotic unipolar depressed patients. These patients showed a normal displacement of the radiotracer $^{123}$I iodobenzamide, supporting that the increased DA release resulted from the amphetamine challenge and not the experimental conditions. Additionally, the amphetamine challenge research did not provide a baseline DA level. Abi-Dargham et al., 2000 addressed this by using an acute DA depletion strategy to observe striatal DA D2 receptor occupation. The results showed a greater increase in receptor availability in schizophrenic patients when compared to control subjects following
the DA depletion. This can be interpreted as a higher level of striatal DA D2 receptors being occupied at a baseline level, further supporting the role of DA D2 receptors in schizophrenia. Interestingly, higher levels of synaptic DA translated to better responses to antipsychotic treatment in patients (Abi-Dargham et al., 2000).

Howes et al., 2013 showed that tyrosine hydroxylase levels, the rate-limiting step in DA synthesis, in the substantia nigra, another brain region dense with DA neurons, were increased significantly when compared to controls. This indicates that schizophrenic patients have a larger capacity for DA production in their DA neurons than their non-schizophrenic counterparts. DA receptors are able to form dimers with one another and there have been many studies examining the effect dimerization may have on the schizophrenic pathology. A 2010 study by Wang et al. reported a 278% increase in D2 homodimers as compared to controls and D2 monomer levels were only 69% of the control level (Howes et al., 2015; Wang et al., 2010). In a study of four schizophrenic individuals, DA D1-D2 heterodimers were increased within the globus pallidus (Perreault et al., 2010), which is bolstered by the earlier post-mortem research by Seeman et al., 1989 showing a reduced inhibitory connection between D1 and D2 receptors in schizophrenic patients. Development of more robust imaging technology like Positron Emission Tomography (PET) and Single Photon Emission Computed Technology (SPECT) has made in vivo experiments much easier to perform and it is expected that more information will become available as studies utilize new imaging technologies. After reviewing all current knowledge, Howes et al., 2015 states that the major DA alteration in schizophrenic individuals is presynaptic, present at the onset of the disorder, and is related to the onset of psychosis. Less
is understood about the effect that DA D1 hypofunction plays within the presentation of schizophrenia. It is thought that a deficiency in prefrontal DA D1 activity could be contributing to cognitive issues seen in schizophrenia (Laurelle et al., 2003).

**Role of PV**<sup>+</sup> **FSIs in Schizophrenia**

In addition to altered glutamatergic functioning, there is also evidence that suggests GABAergic transmission is implicated in schizophrenia as well. More specifically, parvalbumin GABAergic interneurons have been studied in both animal and human models of schizophrenia. Parvalbumin (PV) levels are important for proper neural communication. PV is a high affinity calcium buffering protein, similar in structure to calmodulin and troponin C (Ceilo, 1990; Hontanilla et al., 1998). Importantly, PV is a reliable identifier of a specific subtype of fast-spiking interneurons (FSIs) throughout nervous tissue (Celio, 1990). Varying levels of PV have direct effects on channel distribution and intrinsic excitability of PV fast spiking interneurons (FSIs). Altering PV levels also can manifest in behavioral pathologies affecting cognition, fear conditioning, learning and memory, and neuropsychiatric diseases like schizophrenia.

At the circuit level, PV FSIs alter medial prefrontal cortex (mPFC) output by preferentially inhibiting layer IV and V pyramidal neurons following a cocaine memory reactivation session (Lee et al., 2014; Jorgensen et al., 2019 preprint). PV is paramount for the molecular correlates of learning and memory which includes long-term potentiation within the hippocampus (Donato et al., 2013; Korotkova et al., 2010). Donato et al. showed that networks with low excitatory:inhibitory synaptic density ratios, corresponding to low PV levels, enhance synaptic
plasticity associated with memory consolidation and retrieval. Environmental enrichment promoted the low PV networks while high PV networks were fostered by fear conditioning, leading to a reduction in long-term potentiation and impaired memory consolidation and retrieval (Donato et al., 2013). Additional studies have been conducted to understand the connection between synaptic transmission and behavior. Paired-pulse ratio experiments have shown that paired-pulse depression, normal for wild-type mice, is converted into paired-pulse facilitation in PV knockout mice and concluded that PV is required for the modulation of short-term plasticity (Caillard et al., 2000). Fuchs et al., (2007) have shown that hippocampal dependent tasks, as well as AMPAR-mediated currents, are also reduced in PV knockout mice, affecting glutamatergic transmission and memory retrieval tests. These data provide substantial evidence that PV is important for the underlying mechanisms involved in the behavioral aspects of learning and memory, which is commonly affected in schizophrenia patients.

There is also a growing body of evidence supporting the role of PV in attention. Research by Kim and colleagues found that PV FSIs within the mPFC demonstrated increased and sustained firing during goal-driven attentional processing and elevated activity of PV FSIs predicted successful behavioral execution (Kim et al., 2016). Optogenetic silencing of these cells decreased attentional processing while optogenetic synchronization at gamma frequencies resulted in an increase in goal-oriented behavior and cognition (Kim et al., 2016). Furthermore, they claim that PV FSIs act as the functional unit in coordinating local mPFC circuit activity during goal-driven attentional processing.
Finally, PV dysfunctions are implicated in several neuropsychiatric disorders including schizophrenia. A reduction of layer V PV FSIs in the PFC was observed in impaired working memory tasks of schizophrenic primates (Hashimoto et al., 2010; Cruz et al., 2009; Nakazawa et al., 2012) and human patients (Konradi et al., 2011; Volk & Lewis, 2010). Overall cortical GABA concentrations and GAD activity were also decreased in humans with schizophrenia (Perry et al., 1979; Bird, 1985). This dysfunctional network is hypothesized to start as early as development where GABAergic FSIs play an important part in the maturation of neural circuitry (Nakazawa et al., 2012). Abnormal firing patterns of PV neurons within the hippocampus are also credited for the deficits in memory associated with schizophrenia. Although PV FSIs appear to be involved in schizophrenia, it is still unclear whether altered PV networks is the primary cause of the symptoms or a secondary result of other contributing underlying mechanisms.

**Conclusion**

Schizophrenia is a complex mental disorder that has a high prevalence in young adults and is a major contributor to the global disease burden. The characteristic symptoms of schizophrenia include positive (hallucinations and delusions) and negative (social withdrawal and apathy) symptoms as well as the presence of psychosis. Cognitive impairment, which affects many areas of perception including learning, memory, and attention, is also commonly observed (Fischer & Buchanan 2020). Schizophrenia can present as any combination of the aforementioned symptoms, but the onset of auditory hallucinations and paranoid delusions during early adulthood are most typical (Laruelle, 2014). Current treatments for schizophrenia have had difficulty improving the negative symptoms but Clozapine, a second-generation antidepressant,
has shown efficacy when it comes to treating both positive and negative symptoms in some studies (Kane, 1988; Leucht et al., 2003; Stone et al., 2007).

The molecular basis of the disorder has remained elusive since Philip Seeman and his pioneering research of DA abnormalities in the 1970s (Philip Seeman & Lee, 1975). His research laid the groundwork for the development of the dopamine hypothesis of schizophrenia which posited that dopaminergic abnormalities were responsible for the schizophrenic symptoms. More recent work has specifically identified hyperstimulation of DA D2 receptors in the striatum along with hypostimulation of DA D1 receptors in the cortex as the two main DA abnormalities seen in schizophrenic patients. The effectiveness of antipsychotic medications in treating positive symptoms has led researchers to determine that D2 hyperstimulation is responsible for positive symptoms as many antipsychotics are D2 antagonists. The NMDA receptor hypofunction hypothesis was developed later but has emerged as a potential underlying cause of the DA deficiency. The use of NMDA antagonists has been able to reproduce the dopaminergic abnormalities seen in schizophrenia (Jentsch & Roth, 1999). This finding sparked the idea that the DA dysfunction was not the root of the disorder, but merely a secondary effect from the NMDA receptor hypofunction. Adding to the complexity of mechanistic considerations, PV containing fast-spiking GABAergic interneurons have also recently been implicated in schizophrenia. These GABAergic FSIs play an important role in neural circuit maturation (Nakazawa et al., 2012) and more research will be necessary to determine the exact contributions of PV and FSIs in circuit dysfunction specific to schizophrenia.
Currently, there is no all-encompassing treatment for schizophrenia. However, the future looks bright as the technology available to researchers improves and as our understanding of the disorder deepens. As there are many emerging molecular hypotheses, it is important to consider that schizophrenia is not the result of a single maladaptation, but the combination of many. Investigation into the interplay between DA, glutamate, and NMDA transmission will likely lead to a more thorough understanding of schizophrenia and ideally the development of a treatment that can address this multifaceted disorder.
References


