Firings of a Schizophrenic Mind: Faulty neurotransmission and genetics

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Abstract

Schizophrenia is a common neurological disorder which affects 1.0% of the world population and causes a combination of positive (hallucinations, delusions), negative (anhedonia), and cognitive symptoms. Neuropathology is currently explained by genetics and the dopamine, glutamate, and GABA neurotransmitter theories. The dopamine (DA) hypothesis implicates that hyperactive dopaminergic systems lead to schizophrenia, while compromised DA regulation mimics positive symptoms of schizophrenia. The Glutamate and GABA hypotheses explain the negative and cognitive symptoms of schizophrenia left unexplained by the dopamine hypothesis. Mutations in NMDA-receptor subunits, NR1 and NR2A, are main components of regulating glutamate, while the enzyme GAD regulates GABA neurotransmission. Additionally, several genes, including DISC1, DTNBP1, and NRG3, among many possible de novo copy number variant (CNV) mutations, increase susceptibility to schizophrenia. DISC1 regulates mitochondrial function through mitoflin, while NRG3 influences migration and patterning during neurodevelopment through the production of isofoms. The large number of de novo CNV mutations may also contribute to schizophrenia although individual CNV mutations are rare. While interacting neurotransmitter systems and genetic alterations can lead to schizophrenia, further evidence is required to understand the interactions of these systems and provide insight into a complex neurological disorder lacking a clear source or pathology.

Introduction

Schizophrenia is a complex neurological disease affecting about 0.5-1% of the world’s population and creating social, economic, and health concerns (Park et al. 2010). Schizophrenia mainly affects the dorsolateral prefrontal cortex, cerebellum and striatum of the brain. Since being first diagnosed in the 19th century, the symptoms of schizophrenia have been grouped into three divisions: positive, negative, and cognitive. Positive symptoms are not common to the general population, but are found in the disorder, while negative symptoms are usually found in the general population, but not in the disorder. The positive symptoms of schizophrenia include hallucinations and delusions. The negative symptoms include apathy, anhedonia, and withdrawal. Cognitive symptoms include attention, working memory and executive functions are affected (Hashimoto, 2003). Symptoms usually appear between sixteen and thirty years of age and onset is rarely seen in those over forty-five years old. Schizophrenia is common worldwide and occurs equally among race and gender. While schizophrenia is not overrepresented in any gender or ethnicity, men tend to develop symptoms earlier, and negative symptoms are usually detected before any positive or cognitive symptoms.

Although the symptoms of schizophrenia have been well-recorded, the causes of schizophrenia are varied and not well understood. The possible factors affecting the onset of schizophrenia include both environmental, such as the season born, childhood trauma (Tsuang and Stone 2001), and drug use (Lukoff, 1986); and genetic, such as mutations in key genes affecting neuro pathway. However, many studies suggest that an intricate relationship between genetic predisposition and environmental factors exists (Tienari et al. 2004). Just as the causes vary, the symptoms of schizophrenia also vary between cases and over time (Tandon et al., 2009). This variation makes diagnosis difficult. Diagnosis is currently only done clinically by observing symptoms over six month period. Also due to the mixed symptoms of schizophrenia, treatment, consisting mostly of antipsychotic drugs aimed at correcting neurotransmitter release, is difficult and generally only alleviates the positive symptoms of schizophrenia, leaving the negative and cognitive symptoms unchanged. These antipsychotics have a low tolerability and must be taken over long periods of time, which may increase the risk of detrimental side effects.

Schizophrenia is a complex disorder due to the interaction of many genes and cellular neurotransmission pathways. Although named one hundred years ago, the cause of schizophrenia remains unknown. Understanding the biological basis of the complex neural circuitry in schizophrenia will help to understand the fundamental nature of schizophrenia and develop new treatment and preventive strategies in the future. There are several neurotransmitter systems found to be altered in Schizophrenia, including the widely studies dopamine, glutamate, and GABA neurotransmission systems. Studies have suggested that the dopamine transport system is hyperactive, while glutamate and GABA are hypoactive in pathological conditions. In addition to these pathways playing a potential role in schizophrenia, genetic defects have also been associated with an increased susceptibility for developing schizophrenia. The most consistent genetic link occurs in the genes DISC1, NRG3, and DTNBP1 (McGuire et al, 2008). DISC1 and NRG3 both aid in neuron regulation and development, while DTNBP1 plays a role in neurotransmitter release. In addition to these specific susceptibility genes, many de novo copy number variant (CNV) mutations also occur in schizophrenia due to detrimental microdeletions and microduplications.

The lack of a clear connection between schizophrenia and a genetic or molecular cause has led to many studies over the past decade, in attempt to elucidate possible causes of schizophrenia. These studies will look at genetic mutations in a multitude of genes and deficient neurotransmission of glutamate, dopamine, and GABA. Despite the discoveries of multiple genetic and molecular defects in schizophrenia patients, the connection as to how these changes actually cause schizophrenia are still not speculated. This paper will combine the findings of multiple research articles in attempt to further understand the connection between known genetic and molecular discrepancies and hypothesized pathways of schizophrenia. Based on these findings, we hypothesized that schizophrenia is a result of altered and integrated neurotransmitter signaling that is favored under altered genetics. In order to understand the underlying nature and causes of schizophrenia, we are focusing on three major areas of inquiry in the field: the examination of neurochemical abnormalities, the integration of neurotransmitter systems, and the identification of candidate genes associated with increased susceptibility.
Neurochemical Abnormalities

In this part of our review we will focus on understanding the abnormalities in three main underlying neurotransmitter systems: dopamine, glutamate and gamma aminobutyric acid (GABA). We will connect the major discoveries in the field that showed involvement of neurotransmitter transporters, receptors and catalytic enzymes and how alterations to these systems can result in schizophrenic symptoms.

Dopamine Neurotransmission

Of all the neurotransmitter circuits believed to be involved in schizophrenia, the dopamine theory has been the most enduring. The dopamine (DA) hypothesis suggests that hyperactivity of the dopamine circuit leads to the characteristic symptoms of schizophrenia (Van Rossum, 1966). The first insight into this theory became known when neuroleptic drugs such as chlorpromazine and haloperidol alleviated the schizophrenic symptoms by acting as antagonists for DA D2 receptor sites (Seeman et al., 1976).

Soon after, increased D2 receptors in post-mortem brains of schizophrenia patients (Lee and Seeman, 1977) and increased dopamine occupancy at D2 receptors were also reported (Anissa Abi-Dargham et al., 2000). The dopamine hypothesis was further supported with the finding that drugs like amphetamine (AMPH), DA receptor stimulants, were found to cause schizophrenic symptoms in both humans and in animal models (Angrist et al., 1974; Castner et al., 1999).

Evidence that confirmed the alterations in dopamine levels in schizophrenia led researchers to focus on other molecules that are involved in this neurochemical pathway, such as dopamine transporter (DAT) and catechol-o-methyltransferase (COMT) enzyme, both regulate dopamine activity in the synapses, but through different mechanisms.

The DAT plays a role in locomotion in normal individuals by controlling the dopamine levels in the basal ganglia and nucleus accumbens (Giros et al., 1996). In 1996, Giros and his colleagues found out that mice lacking DAT (DAT-KO) were unable to re-uptake released DA (Giros et al., 1996) leading to hyperdopaminergia. These knockout mice also exhibited hyper-locomotion, which could be reversed by administration of DA receptor antagonists (Giros et al., 1996).

COMT is an enzyme involved in monoamine metabolism (Williams et al., 2007) and is expressed mainly in the prefrontal cortex where it is found to be involved in dopamine metabolism. When COMT is inhibited in mice, their extracellular DA levels were found to be increased supporting the idea of possible alteration in DA activity in schizophrenic brain (Tunbridge, 2004). Recently, it was found out that frontotemporal function during verbal function modulated by COMT is altered in Schizophrenia patients (Prata et al., 2009). A study that immediately followed found that the COMT and DAT genes interact nonadditively to regulate executive functions. This effect is altered in schizophrenia which might be leading to the abnormal hyper activity of dopamine (Prata et al., 2009).

These data support the idea that dopamine neurotransmission is altered in schizophrenia. However, the dopamine hypothesis alone does not explain all the symptoms underlying schizophrenia, suggesting that involvement of one or more neurochemical systems. With the possibility of many neurotransmitters involved in schizophrenia, the dopamine hypothesis has been modified.

Glutamate Neurotransmission

Glutamate dysfunction in schizophrenia was first discovered when phencyclidine (PCP) and ketamine were found to closely mimic Schizophrenia (Luby et al., 1959). The PCP mimics the negative symptoms of schizophrenia far better...
than other drug-induced psychoses such as those induced by amphetamine (Gaw and Snyder, 2002). In the late twentieth century many studies found that PCP, ketamine act as noncompetitive antagonists of NMDA receptors (Javitt and Zhukin, 1991; Ellison, 1995; Malhotra et al., 1997). Soon after, many animal models were used to understand the nature of the disease (Carlsson, 1990; Corbett et al., 1993). A study done in mice models by Mohn and colleagues further support the evidence of glutamate receptor deficiency that leads to schizophrenia. In their study, they created mice with only 5% –10% of normal levels of the essential NR1 subunit of NMDA receptor. The mice displayed increased motor activity, stereotypy, and abnormal social and sexual interactions. They also found that these symptoms could be attenuated by administering haloperidol or clozapine, an antipsychotic medication (Mohn et al., 1999).

Another study by Yee and colleagues, it was shown that GABA, receptor 3 knockout mice show positive symptoms associated with hyperdopaminergic activity (Yee et al., 2005). This might be due to the absence of inhibitory effects on dopamine neurons might be leading to hyperactivity.

All of these studies together suggest that hypofunction of NMDA receptors as a possible starting point that will lead to alterations in many neurotransmitter systems. Current evidence in the field suggests the crucial role of glutamate hypothesis in understanding the nature of schizophrenia. Recent studies have given us the opportunity of putting the puzzle pieces together and make a unified theory to explain molecular mechanisms underlying the disease. By combining the studies that have been done we can conclude that hypo-activity of NMDA receptor leads to less glutamate levels leading to a decrease in GABA synthesis. Altered GABA levels will result in hyperactivity of the dopamine neurotransmission. The possible interaction of the pathways that lead to schizophrenia is shown in figure 1.

Role of genetics in Schizophrenia

In this part of our review we will focus on candidate genes that are found to be involved in onset of schizophrenia. 

**DISC1 isofrm regulation and mitochondrial interaction**

The disrupted-in-Schizophrenia 1 gene (DISC1) gene is involved in neurodevelopment, regulating neurite growth, neuronal migration, and neurogenesis (Nakata, 2009). Although found in both the hippocampus and lymphoblasts, DISC1 is found in different forms. The DISC1 differs between these locations because different isoforms are created through the splicing of exons. The isoforms in DISC1 include a missing exon3, missing exon7 and 8, and an exon3 insertion variant; each creating truncated DISC1 mRNA (Nakata et al., 2009). The production of these DISC1 isoforms is thought to be due to changes in gene processing during DISC1 splicing, forming aberrant or truncated DISC1 mRNA. In the hippocampus of schizophrenia patients, as well as during fetal development, DISC1 is more commonly found in the truncated isoforms. The truncated DISC1 in the hippocampus does not have the C-terminal region that is thought to be necessary for proper neurodevelopment. This may cause a deficit in neurodevelopment which may lead to amount of GABA neurotransmission in the affected brain areas of schizophrenia patients. Studies have also shown that decreased levels of glutamic acid decarboxylase (GAD), an enzyme is important in the conversion of glutamate to GABA, in schizophrenic patients (Fatemi et al., 2005). Together, these studies explain the cognitive symptoms of schizophrenia due to decreased GABA neurotransmission.

**Integration of Neurotransmitter Systems**

Given the roles of each neurotransmitter system in Schizophrenia, we are trying to understand how all three of these circuits would interact with each other in order to develop positive, negative, and cognitive symptoms of schizophrenia. Many studies done over the past decade addressed this question.

As mentioned earlier, the NMDA-R1 receptor knockout for glutamate leads to schizophrenia (Mohn et al., 1999). A study that was immediately followed showed that there were higher levels of dopamine in postmortem brain tissues of the striatum and the frontal cortex. These mice also displayed symptoms such as increased locomotor activity and cognitive deficits. Further, these effects could be alleviated by treatment with antipsychotics (Miyamoto et al., 2000). Recent findings also suggest that early postnatal inhibition of NMDAR activity in GABAergic inter-neurons contribute to the pathophysiology of schizophrenia (Belforte et al., 2010).

In a study done by Yee and colleagues, it was shown that GABAA receptor c3 knockout mice show positive symptoms associated with hyperdopaminergic activity (Yee et al., 2005). This might be due to the absence of inhibitory effects on dopamine neurons might be leading to hyperactivity.
the onset of schizophrenia in patients who have disrupted processing of DISC1. Although the effects of DISC1 are known, the mechanism by which DISC1 leads to schizophrenia has only recently begun to be understood.

DISC1 has been found to play a role in mitochondrial regulation through direct interaction with mitofilin (Fig. 2), an essential mitochondrial inner membrane protein (Gieffers et al., 1997; Park et al., 2010). Reducing the levels of functional DISC1 induces dysfunction in mitochondria, causing reduced levels of ATP, disrupted Ca²⁺ dynamics, and decreased monoamine oxidase-A (MAO-A) production (Park et al., 2010). As mentioned previously, the truncated DISC1 isoform is found to be increased in schizophrenia, leaving less functional DISC1 to act in the neuron. This leads to a decreased interaction between DISC1 and mitofilin in the mitochondria, resulting in deregulation of mitochondrial functions (Park et al., 2010). The mitochondria have been associated with schizophrenia through the synthesis of MAO-A, a preliminary molecule to dopamine, which, as mentioned earlier, plays a vital role in neurotransmission (Ben-Shachar, 2004). As the regulation of the mitochondria decreases in response to a decrease in DISC1-mitofilin interaction, the mitochondria produce less MAO-A resulting in less dopamine production. With less dopamine in the neuron, neurotransmission is hindered, and the risk of developing schizophrenia is increased (Park et al., 2010).

**DTNBP1 regulation of neurotransmitter release**

As schizophrenia has many possible causes, multiple genes have been found to increase susceptibility to the disorder. Another one of these potential genes is DTNBP1, which codes for the protein dystrobrevin-binding protein 1 or dysbindin. Dysbindin has been associated with schizophrenia through its assistance in regulating neurotransmission. In patients with schizophrenia, a decrease in levels of dysbindin in the hippocampus and prefrontal cortex is thought to result in cognitive impairment (Weickert et al., 2008; Chen et al., 2008) and is associated with glutamate and dopamine neurotransmission in the hippocampus (Numakawa et al., 2004; Kumamoto et al., 2006). The effects of dysbindin were studied by using sandy (sdy) mice as a model due to its interesting lack of dysbindin expression (Li et al., 2003). Amperometric and electron microscopy studies showed that dysbindin regulates the amount of secretion, the release probability, and the kinetics of synaptic vesicles by regulating the fusion step of exocytosis (Chen et al., 2008). This study also showed that the kinetics of vesicle release were altered in hippocampal nerves in sdy mice due to the loss of dysbindin alone (Chen et al., 2008). These results suggest that decreased levels of dysbindin could cause cognitive symptoms of schizophrenia symptoms by affecting the transmission of neurotransmitters. Other studies have shown that dysbindin is associated with negative symptoms of schizophrenia (DeRosse et al., 2006). As a result of dysbindin’s role in neurotransmission, genetic variations in DTNBP1 may decrease the level of dysbindin present at the synapses of neurons (Fig. 2). This reduction of dysbindin may induce altered vesicle trafficking leading to impaired neurotransmission, and ultimately the negative symptoms associated with schizophrenia.

**Neuregulin isoform affects symptoms in Schizophrenia**

A third susceptibility gene, NRG3, encodes the protein neuregulin which has been shown to play a role in...
neurodevelopment in the cerebral cortex by aiding in cell migration and patterning (Balciuniene et al., 2007). NRG3 interacts with NRG1, ErbB4, and AKT1 to form a complex in the NRG-ErbB signaling pathway. NRG3, similarly to DISC1, goes through complex splicing to form many different isoforms that are developmentally regulated and pathologically increased in schizophrenia (Kao et al., 2010). This suggests that some variations in neuregulin may be associated with onset of schizophrenia, making NRG3 another susceptibility gene. Indeed, studies have shown that several isoforms of NRG3 are associated and elevated in the schizophrenic brain (Carteron et al, 2006). Although previously discovered genes mostly affected one classification of symptoms, NRG3 isoforms can affect positive, negative, or cognitive symptoms (Chen et al., 2009; Kao et al., 2010). Increased expression of NRG3 can lead to deficient neurodevelopment and possibly less neurotransmission (Fig. 2).

Rare de novo CNV’s associated with schizophrenia

Schizophrenia can exist in familial form, in which genetic mutations are passed from parent to offspring, and sporadic form, in which the mutations occur independently of the parents’ genetic makeup. In schizophrenia patients, many small, de novo copy number variants (CNV) create microdeletions and microduplications. These mutations in the genome can affect genes that are associated with the disease, increasing the susceptibility of developing schizophrenia. In recent studies, CNV’s were found to be more common in early onset schizophrenia (Xu et al., 2008). These studies suggest that schizophrenia can be caused by rare mutations affecting neurodevelopment and regulation pathways in the brain, such as the glutamate receptor and neuregulin signaling. As neurodevelopment contains hundreds of proteins, there are many possible mutations that will alter pathways and affect neuronal development and regulation. While each of these mutations may not occur often, the large number of different possible mutations may contribute to a significant portion of the total cases of schizophrenia. Further research of de novo CNV mutations may lead to the discovery of more genes that are involved in neurodevelopment pathways, such as the NRG-ErbB pathway, and neurotransmission pathways, including the dopamine, glutamate, and GABA neurotransmitters. Many mutations have already been identified and connected to schizophrenia through the discovery of de novo CNV mutations in schizophrenia (Stefansson et al., 2008).

Future Research

Understanding the etiology of Schizophrenia is one of the challenges that the scientific community has faced. The recent convergence of neuropathological, neurochemical, and genetic studies may lead us to understand the molecular basis and causes of schizophrenia. Possible future studies would aim at further elucidating the interactions between genetic variations, neurotransmitter pathways, and environmental factors in order to find a link between the altered neurotransmission pathways and candidate genes in hopes of gaining insight to finding the cause of the disease. Previous studies have shown that genetic predispositions may not have an effect unless environmental pressures are present. Twin studies can help to elucidate selective environmental pressures associated with schizophrenia. Other than the complex role environment plays in the development of schizophrenia, protein-protein interactions may also add complexity to the pathological mechanism. As in the NRG-ErbB signaling complex, one protein variation among any of the proteins in the complex may lead to the same detrimental effects that would be seen if another of the proteins in the complex was varied. By understanding which protein ultimately caused detrimental effects leading to disease onset, we may be able to link the source and outcome of deficient pathways. Apart from the neurotransmitter pathways that are mentioned in this article, serotonin neurotransmission has also been found to be altered and found to be hyper-activated under decreased levels of NMDA receptors (Miyamoto et al., 2001). To understand the nature of the disease, it is necessary to combine the neurotransmission systems.

While presenting many challenges to study, schizophrenia affects the most unique human characteristics of ours: these higher order skills make it difficult to create a suitable animal model. Therefore, drawing conclusions about the disease should rely on neuropharmacology, neuroimaging, and genetic studies until a model with measureable phenotypes is created.

Conclusion

After over one hundred years since it was named, the cause and biological basis of schizophrenia remains unknown. Involvement of many different neurotransmitter systems and genes has advanced our understanding about the disease over the past decade. The current evidence suggests that schizophrenia does not have one central cause but instead, a combination of several neurotransmitter pathway alterations and disrupted genetics.

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