Schizophrenia is a severe brain disorder affecting 1% of Americans. Symptoms include delusions, hallucinations, and thought and movement disorders, all of which normally develop during the late teens or early twenties. Risk factors are various and widespread, including genetic, environmental, and biochemical factors. This review will focus on the three main biochemical hypotheses behind schizophrenia, each hypothesis highlighting one of the main neurotransmitters involved in schizophrenia: dopamine, glutamate, and GABA. The dopamine hypothesis, the oldest of the three, suggests dopamine to be excitatory to cells, thus leading to the symptoms seen in schizophrenia. The glutamate hypothesis suggests cortical dysfunction with particular involvement of NMDA receptors throughout the brain affecting glutamate. The most recently developed hypothesis involves GABA, linking defects in the GABA system to cognitive dysfunction. Despite all the current research on schizophrenia, there is no curative treatment yet available, only medications that aid to address symptoms. One widely used form of treatment is the use of antipsychotics, which function to alter the level of neurotransmitters in the brain. Future studies aim to look into how alterations in the other two neurotransmitters, glutamate and GABA, can be utilized for treatment, further expanding upon the theory of a genetic linkage in the disease.

Introduction

The word “schizophrenia” has been in use for less than 100 years. However, the disease has been in existence since long before that. In 1887, a German physician, Dr. Emil Kraepelin, first identified the disease to be a distinct mental illness. Dr. Kraepelin described his patients as having symptoms of “dementia praecox,” or premature dementia, symptoms we now associate with schizophrenia. Dr. Kraepelin studied young adults with dementia, saying this form was “early” compared to Alzheimer’s or other forms of dementia (Kraepelin, 1890; Kraepelin, 1909). The term “schizophrenia” came about in 1911, when a Swiss psychiatrist, Dr. Eugene Bleuler, changed Kraepelin’s misleading name to “schizophrenia.” Dr. Bleuler observed that the disease was not a dementia and could occur both early and late in life. The word “schizophrenia” translates to split-mind, which Dr. Bleuler used to describe the altered thinking patterns of patients with the disease (Bleuler, 1950).

Schizophrenia is divided into five categories: disorganized, catatonie, paranoid, residual, and undifferentiated. These categories are not always reliable, and it is difficult to diagnose and predict the outcomes of the different types. Today researchers make use of the positive and negative symptoms, first identified by Dr. Bleuler, to predict the type and severity of the disease. Positive symptoms include delusions, hallucinations, and thought disorderization. Negative symptoms include disruptions of normal emotions and behaviors (Kring et al., 1993). Symptoms of schizophrenia usually never develop before puberty or after age 40 and affect around 3.2 million Americans (Lewis & Lieberman, 2000). There are many factors that may contribute to schizophrenia, including environment, genetics, and biochemical factors.

Exposure to toxins, stress, and autoimmune or traumatic insults are theorized to subtly alter neurodevelopment, increasing vulnerability to schizophrenia (Marcelis et al., 1998). Other factors, such as place and season of birth have also been shown to contribute to the risk of schizophrenia (Mortensen et al., 1999). What separates schizophrenia from other disorders is that there are no immediate consequences of schizophrenia; rather, individuals seem to function normally until they enter a period of risk later in life, usually in late adolescence or early adulthood. (Lewis, 1997; Janskog et al., 2000; Raedler et al., 1998).

Genetics also play a role in schizophrenia. While the chance for developing schizophrenia in the general population is 1%, the risk increases up to ten times for siblings or children of individuals with schizophrenia. Twin studies have suggested a heritability component between 83% and 87% (Cardno et al., 1999). More specifically, there are multiple chromosomes, including chromosomes 1, 6, 8, 10, 13, and 22, that have potential sites of vulnerability (Pulver, 2000). Within these sites of vulnerability, particular suspect genes have been linked to schizophrenia and have been associated with an increased risk when mutated (Millar et al., 2005). These suspect genes include DISC1, PDE4B, GAD1, FEZ1, and COMT, all of which are involved in mood, memory, and cognitive function—areas that are altered in schizophrenia (Millari et al., 2005; Straub et al., 2007; and Sakae et al., 2008).

The last contributing factor to the development of schizophrenia includes the biochemical basis theory, which is concerned with the role of neurotransmitters and their receptors. Dopamine, glutamate, and GABA are the three main theories and will be discussed in depth later in this paper. The dopamine hypothesis states that psychotic symptoms of schizophrenia are related to heightened dopamine levels in the brain, resulting from an increased amount of D2 receptors (Davis et al., 1991). The glutamate hypothesis states the hypofunction of NMDA receptors leads to elevated cortical glutamate inducing symptoms of schizophrenia. Lastly, the GABA theory states that the absence of GABA’s inhibitory function causes an imbalance of increased dopamine and glutamate, which in turn gives rise to the psychotic symptoms of the disease.

Dopamine

The dopamine hypothesis, the most established and oldest hypothesis behind schizophrenia, was first proposed by Dr. J. Van Rossum in 1966. The classic hypothesis proposes that certain dopaminergic pathways are overactive in schizophrenia (Mathysse, 1974; Meltzer & Stahl, 1976; Van Rossum, 1967). This hypothesis received support from the correlation between clinical doses of antipsychotic drugs and their effectiveness in blocking dopamine D2 receptors and from the psychosis-inducing effects of dopamine-enhancing drugs (Creese et al., 1976; Seeman & Lee, 1975; Liebermann et al., 1987). Later studies looked deeper into this classic theory, developing a revised dopamine hypothesis. The revised hypothesis proposes that reduced striatal inhibition on the thalamus will lead to increased psychomotor activity and sensory input. Dopamine is excitatory, and thus behaviorally stimulates via direct pathways (Davis et al., 1991).

Antipsychotics have been found to be effective in treating the symptoms of schizophrenia, improving the prognosis of schizophrenia dramatically by acting as an antagonist at the D2 receptor. It has thus been proposed that altering dopamine at this receptor may play a role in the physiological processes of schizophrenia (Seeman et al., 1976). To explore the occupancy of D2 receptors by dopamine in humans, Arbi-Dargham et al. (2000) measured the baseline D2 receptor availability during acute dopamine depletion. The results of this study found in vivo evidence that dopamine occupies a larger portion of striatal D2 receptors in patients with schizophrenia compared to controls. This gives support for a better response towards antipsychotic treatments to help alleviate the positive symptoms of schizophrenia. In 2004, Hirvonen et al. expanded this study and found that in a subpopulation of schizophrenia patients, the increase in D2 receptor binding may be genetically determined, providing support for a major antipsychotic drug target.

While antipsychotics have been shown to alleviate some of the positive symptoms of schizophrenia, the cognitive symptoms were more difficult to analyze. Kellendonk et al. (2006) aimed to explore the relationship between D2 receptor density and cognitive deficits in mice by studying mice with increased D2 receptors. The results suggest that an over-expression of D2 receptors leads to difficulties in memory-related tasks. D2 receptors were shown to affect D1 receptor activation in the prefrontal cortex, a structure involved in working memory, suggesting alterations in the prefrontal cortex may be responsible for the cognitive deficits seen in schizophrenia.

Since the discovery that dopamine release occurs in particular target areas, such as the prefrontal cortex, there have been suggestions that DA neuron diversity occurs in an anatomically ordered fashion. Lammel et al. (2008) aimed to explore this theory by studying properties of the mesocorticolimbic vs mesostriatal dopamine system. The results provide evidence that the dopamine midbrain system is comprised of two types of DA midbrain neurons with very different properties. The study found a fast-firing subtype of DA neurons which expressed the plasma membrane dopamine transporter, DAT, at very low levels. The fast-firing DA neurons that projected to the prefrontal cortex were found to contain no D2 autoreceptors and were also shown to express low mRNA levels of D2 receptors. This study provides another potential therapeutic target in application to...
the dopamine systems involved in schizophrenia. Schizophrenia was once considered to be a “dopamine disorder,” however, in recent years this perception has changed, and now two other neurotransmitters are part of the larger picture of schizophrenia: glutamate and GABA.

**Glutamate**

Over the last 20 years, limitations of the dopamine model have become increasingly apparent, necessitating development of alternative models. Because NMDA receptors are located throughout the brain, glutamatergic models predicted widespread cortical dysfunction with particular involvement of NMDA receptors in the brain. An alternative to the dopamine hypothesis was first proposed in the early 1990s, based upon the observation that phencyclidine (PCP) and ketamine, by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors, lead to elevated cortical glutamate, an excitatory neurotransmitter (Nikki et al., 1995). The PCP and ketamine bind to the NMDA intrachannel site of the receptor and thus preventing calcium ion flux into the cell (Anis et al., 1983), leading to symptoms seen in schizophrenia including hallucinations, delusions, and thought disorder.

NMDA receptor blockade in the anterior thalamus could be the main site leading to cortical glutamate release, and cortical excitotoxicity, since injection of the selective and specific NMDA receptor antagonist MK-801 into the anterior nucleus of the thalamus induced cortical degeneration in a pattern from systemic administration, while injection directly into cortical regions did not lead to any neurodegenerative changes (Sharp et al., 2001). The amount of glutamate detected in human patients was made possible by the advance technology of magnetic resonance spectroscopy (MRS) (Theberge et al., 2002). Using this MRS elevation of glutamine and found in humans following ketamine administration (Rowland et al., 2005). The glutamate hypothesis proposes the hypofunction of NMDA receptors prevents glutamate from binding to the receptor increasing excitotoxicity glutamate levels, which induce schizophrenia symptoms. Phencyclidine, PCP, has been shown to act as an antagonist for glutamate receptors prevention of affinity for glutamate (Nikki et al., 1995). Agents that indirectly enhance NMDA receptor function via the glycine modulatory site reduce negative symptoms and improve cognitive function (Seasack et al., 2003). Over the last 20 years, limitations of the dopamine model have become increasingly apparent, necessitating development of alternative models. Because NMDA receptors are located throughout the brain, glutamatergic models predicted widespread cortical dysfunction with particular involvement of NMDA receptors in the brain. An alternative to the dopamine hypothesis was first proposed in the early 1990s, based upon the observation that phencyclidine (PCP) and ketamine, by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors, lead to elevated cortical glutamate, an excitatory neurotransmitter (Nikki et al., 1995). The PCP and ketamine bind to the NMDA intrachannel site of the receptor and thus preventing calcium ion flux into the cell (Anis et al., 1983), leading to symptoms seen in schizophrenia including hallucinations, delusions, and thought disorder.

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NMDA receptors are located on brain circuits that regulate dopamine release, suggesting that dopaminergic deficits in schizophrenia may also be secondary to underlying glutamatergic dysfunction (Seasack et al., 2003).

**GABA**

The first person to suggest a role for GABA in the pathophysiology of schizophrenia was Eugene Roberts in 1972. He suggested that because GABA’s function as an inhibitory neurotransmitter was to modulate brain levels, an absence of it would cause an influx in dopamine (Garbutt et al., 1983). However, due to a lack of both biochemical and pharmacological evidence, a clear connection between the disease and the neurotransmitter could not be made. This changed in 2006 when Lewis et al., conducted postmortem brain studies on schizophrenia individuals and showed recurring defects in GABAergic pathways along with reduced mRNA for GAD67. This major finding solidified the GABA hypothesis and allowed researchers to move forward and build upon the theory. One study demonstrated a decrease in specific fast spiking GABA interneurons that respond to sudden changes in brain activity (Huang et al., 2007; Pilai et al., 2008). Other studies have shown that dysfunction in GABAA and GABAB receptors are prevalent in schizophreniand are normally associated with a wide variety of behavior processes (Rudolph et al., 2004). Current studies now mainly focus on the reduction of GAD67 mRNA and the genetics that tie into schizophrenia.

The protein GAD67 is a key enzyme in the biosynthesis of GABA. It actively converts glutamate into GABA and is encoded by the GAD1 gene (Kehne & Maynard, 2012). When looking into how this protein is related to schizophrenia, research has shown that lower levels of GAD67 have been noted within the prefrontal cortex (PFC) in patients in comparison to healthy individuals (Straub et al., 2007). Even more significant, these researchers found that reduced GAD1 mRNA levels were directly related to a single nucleotide polymorphisms (SNP) found within the GAD1 encoding region across several individuals (Straub et al., 2007). This evidence supports the genetic linkage between the disease and GABA, which was suggested in 2007 when a gene mainly found within GABAergic neurons, FEZ1, was knocked out mice (Sakae et al., 2008). The experimental group instantly developed hyperactivity and hypersensitivity to an over release of dopamine, parallel to human schizophrenia individuals. The findings in this study led other researchers to suggest an interaction mechanism between GABA, glutamate and dopamine: when the protein GAD67 is absent, and glutamate is not converted into GABA, there is no regulation of dopamine...
Models of Schizophrenia

It is extremely difficult to study the molecular biology and to generate genetic models of mental illnesses as there is limited knowledge of the underlying anatomical, physiological, and genetic substrates involved in these diseases. Disorders that only affect one gene, such as Huntington’s disease, are easier to study than mental disorders, which tend to be polygenic and more complex. Therefore, for schizophrenia, it has been extremely difficult to create animal models that model all aspects of the disease.

One model that has been used in recent years to model schizophrenia was created with the use of phenyclidine, or PCP. PCP has been shown to induce symptoms similar to those experienced in schizophrenia. PCP was first developed for use as a surgical anesthetic; however, after use patients would experience hallucinations, delirium, and disordered behavior (Morris et al., 2005). PCP is of major interest to neuroscientists because it not only models the positive and negative symptoms of schizophrenia, but also models some of the cognitive deficits commonly present (Adler et al., 2014). Thus, PCP has been used to create effective in vivo models of schizophrenia. Acute administration of PCP in rats has been shown to impair cognitive and behavioral functioning (Mansbach & Geyer, 1989), proving to be an effective tool in modeling the symptomatology of schizophrenia.

While the future for animal models of schizophrenia is not certain, there is hope that models will be created to allow for the study of disease mechanisms and for investigation into new potential treatment options, which will prove to be a tremendous tool in the field of schizophrenia research.

Conclusion

Schizophrenia is a complex mental disorder that is characterized by various positive and negative symptoms such as anxiety, hallucinations, and reduced social engagement. The direct cause of this disorder is not well known, but several factors such as genetics, environment, and cellular processes have been correlated to its development. By examining these factors through the lens of the three neurotransmitters dopamine, glutamate, and GABA, one is able to better understand the pathophysiology of the disorder and look towards creating more effective treatments and models to help advance schizophrenia research. This advancement will not only help those who suffer from schizophrenia, but it could help better understand other like-disorders that are affecting the CNS such as bipolar and anxiety disorders.

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