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Short Communication

Dopamine Supersensitivity in Schizophrenia

Bolu Oladini*

Department of Neurology, University of Illinois at Chicago, USA

***Corresponding Author:** Bolu Oladini, Department of Neurology, University of Illinois at Chicago, USA.

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Schizophrenia is a mental illness that is extremely debilitating. It is not very well understood but has a large effect on society. The disorder has adverse effects on work, school, and social functioning, among other things. Additionally, patients who are diagnosed with schizophrenia die 12 to 15 years earlier than the average person [1]. When that fact is combined with the overall prevalence of the condition being 1% as of 1997, it becomes evident that schizophrenia has an enormous burden on society [2].

The illness is a psychotic syndrome characterized by a duration of longer than 6 months, and patients exhibit a wide variety of symptoms [3,4]. Unfortunately, there is no objective test to determine if someone has schizophrenia, so diagnosis is based on confirming the symptoms and ruling out other potential causes. The DSM-V diagnostic criteria require that patients have a social or occupational dysfunction, and symptoms must have been present for six months and include one month of active symptoms [5]. Positive symptoms include hallucinations, delusions and disordered thoughts. Negative symptoms include blunting of emotions, social withdrawal, and self-neglect. Cognitive dysfunction is also common.

The course of schizophrenia has been explained through the stress-vulnerability model [3]. This model states that the first step towards the disorder is a vulnerability, which comes from genetics and early childhood experiences. This alone is not enough to cause the illness, however. According to this model, stress, coping skills, and social support are the most important factors to prevent schizophrenia. It is also important for the person to engage in structured, meaningful activity, because this lowers stress.

No specific genes have been identified that directly cause schizophrenia, but several genes have been associated with an increased risk. Most recently, alterations in the gene that encodes the C4 complement protein has been linked with schizophrenia. The mechanism seems to be related to the synaptic elimination that occurs in adolescence and early adulthood. Developmentally, these are the time periods in which schizophrenia is most likely to appear, and the C4 protein plays a significant role in the synaptic elimination process [6].

Other than genetics, there are many different risk factors for schizophrenia, and there are not many similarities between them. Research has shown that some immigrant ethnic groups are at a higher risk for developing the condition compared to native-born people [7]. The most likely explanation for this phenomenon is that immigrants have the additional stress of assimilating to the culture and learning a new language, so stress is likely the underlying risk factor. Living in an area where there are fewer members of your culture is also stressful, so this is likely the reason that the risk for schizophrenia in immigrant groups increases if they live in an area where there are fewer members of their culture [8]. Cannabis use is a factor that has been shown to increase the risk for psychotic disorders [9]. Lack of oxygen at birth, brain lesions, stress, isolation, and too much caffeine have been linked to higher rates of schizophrenia [10]. Importantly, the signs and symptoms of the disease are the same regardless of the cause. This suggests that there may be a commonality to all of these risk factors that predisposes people to schizophrenia.

The main thing that the majority of schizophrenia patients have in common is a behavioral supersensitivity to drugs similar to dopamine, such as amphetamine or cocaine [10]. This occurs regardless of whether or not the patient is taking antipsychotic drugs. According to the results of one study, up to 78% of subjects with schizophrenia had new or intensified psychotic symptoms after being given amphetamine or methylphenidate. This occurred in only one quarter of control subjects. Since amphetamine causes increased release of dopamine from the neuron terminals, there are two possibilities: either there is increased release of dopamine in schizophrenia, or the postsynaptic receptors are supersensitive to dopamine.

Antipsychotic medications have been the mainstay of schizophrenia treatment for decades [4]. The first class of antipsyc-

hotics, discovered in the 1950's, includes haloperidol and chlorpromazine. These drugs were effective at reducing the psychotic symptoms of the disorder, but often led to motor side effects such as tardive dyskinesia. The second generation of antipsychotics, termed "atypical", were introduced to the market within the past 20 years. These drugs include risperidone, olanzapine, quetiapine, ziprasidone, and aripirazole. They have been shown to have a lower incidence of motor side effects, but have several metabolic side effects. These include diabetes, weight gain, increased triglycerides, and increased cholesterol.

The D2 receptor is the most common target for antipsychotic drugs [10]. It seems that this feature is necessary for antipsychotic action. Five different types of dopamine receptors have been found: D1, D2, D3, D4, and D5. Research has found no correlation between clinical doses of antipsychotics and their affinities for D1 or D5. Also, D3 and D4 are not consistently targeted by antipsychotic drugs, therefore they cannot be clinically relevant to the mechanism of action [10]. It has been shown that the majority of antipsychotics have high occupancy at the D2 receptor (above 70%). Further research using positron emission tomography (PET) has shown that the optimal D2 receptor occupancy is 60-65% for antipsychotic response, while an occupancy of greater than 80% leads to an increased likelihood of extra-pyramidal symptoms [11].

The fact that the clinical effect of antipsychotic drugs is tied directly to their affinity for the D2 receptor suggests that something about the receptor is abnormal in schizophrenia [10]. Dopamine has different affinities for the two different states of the receptor. It binds to $D2^{high}$ when the concentration is below 100 nm, and it binds to $D2^{low}$ when the concentration is higher than 100 nm. Research has found that the functionally active state of the D2 receptor is $D2^{high}$. If the density of $D2^{high}$ receptors was elevated in schizophrenia, it would help provide an explanation for the fact that up to more than 70% of all patients with the condition are supersensitive to dopamine [12].

Several animal models have attempted to answer the question of whether $D2^{high}$ states are elevated in schizophrenia [10]. One model used amphetamine to induce dopamine supersensitivity, and the overall D2 receptor density in the brain striatum was normal. However, the $D2^{high}$ receptors were 250% higher than normal. This same type of $D2^{high}$ elevation has been shown in other animal models of psychosis. For example, researchers used a metabotropic glutamate receptor-2 (mGluR2) gene knockout to make mice supersensitive to dopamine, and the brain striata of these mice showed an increase in $D2^{high}$ receptors of 300-400%. Deletions of GABA and other non-dopamine genes have also been shown to increase $D2^{high}$ states of the receptor, causing dopamine supersensitivity. Although measurements have not yet been done in humans, it seems that an elevated state of $D2^{high}$ receptors is possibly the major underlying risk factor for schizophrenia. Imaging tests using radioactive $D2^{high}$ agonists will be required to definitely prove this. Even though the elevation of $D2^{high}$ receptors seems to be required for schizophrenia, twin studies have shown that factor alone is not enough to cause the full disease.

Although antipsychotics are the mainstay of treatment for schizophrenia, there are some conflicting results on whether or not they improve patient outcomes in the long run [13]. The trial that proved the efficacy of antipsychotics was conducted by the National Institute of Mental Health about 50 years ago. They enrolled 344 patients, and at the end of 6 weeks, 75% of them were "much improved" compared to 23% of placebo patients. However, 3 years later, the researchers conducted a follow-up. The placebo patients were less likely to be re-hospitalized than any of the subjects that had received a phenothiazine antipsychotic. This suggests that while the drugs were effective in the short term, perhaps they put the patient at higher risk for subsequent psychosis and re-hospitalization. The researchers then conducted withdrawal studies, and found disturbing results. The higher dose of medication the patient was on, the more likely he or she was to have a relapse.

The explanation for this phenomenon relates back to the D2 receptor [13]. When a patient is taking antipsychotic medication, 60-80% of his or her D2 receptors are blocked. To adapt to this, the brain increases the density of the D2 receptors. This causes dopamine supersensitivity, which is a major risk factor for psychosis. The patient is at an especially high risk of relapse if he or she suddenly stops taking the medication. The dopamine supersensitivity is the brain's way of opposing the effect of antipsychotic medications, and once the medication is discontinued, things are out of balance.

Discontinuation of these drugs can be especially problematic. One researcher has postulated that new onset psychosis can occur as a part of the withdrawal process of antipsychotics, rather than because of the underlying condition [14]. Some of the clearest evidence of this is the fact that new onset psychosis has occurred in people without a previous history of psychiatric illness. Also, the quickness of onset of the symptoms after drug withdrawal also points to the fact that the psychosis is related to withdrawal process.

Part of the problem is that when patients withdraw from these medications, the new onset of psychotic symptoms is attributed to the schizophrenia [14]. This is then used as further evidence to

continue antipsychotic treatment, which leads to even worse outcomes in the end. Instead of continuing this vicious cycle, there needs to be a new approach to long-term treatment and a focus on safe discontinuation of these medications. Jonathan Cole, who was a major early figure in psychopharmacology, made a statement that "an attempt should be made to determine the feasibility of drug discontinuance in every patient" [13]. Guidelines on safe withdrawal from antipsychotics need to be established so that patients can discontinue these medications without the risk of rebound psychosis.

The World Health Organization conducted a study in 1969 that supports this theory [13]. They looked at outcomes for patients with schizophrenia in the US and 4 other developed countries and compared them to patients in developing countries (India, Colombia, and Nigeria). Surprisingly, the patients in the developing countries were doing much better at 2-year and 5-year follow ups. There were 64% of patients that were without symptoms and functioning well in the developing countries, compared to only 18% in the developed countries. What made the difference? In the poorer countries, doctors kept patients on antipsychotics only 16% of the time. But in the developed countries, doctors maintained patients on antipsychotics 61% of the time.

MRI studies have also corroborated the theory that antipsychotics lead to worse long-term outcomes for schizophrenic patients [13]. Researchers have found that these drugs actually cause atrophy of the cerebral cortex and increase the size of the basal ganglia. Another group of researchers found that the enlargement of the basal ganglia due to antipsychotics results in schizophrenic patients having more severe positive and negative symptoms. So, over the long term, these drugs cause the symptoms to get worse, instead of better. When you add the risk of diabetes, obesity, tardive dyskinesia, and other side effects of these drugs, it becomes clear that antipsychotics are not the solution for long-term treatment of schizophrenia.

A group of researchers in Europe have developed a few programs with the goal of minimizing the use of antipsychotics, and their results have been very good [13]. In one study, 55% of first-episode schizophrenic patients were completely off medications at the end of 3 years. The rest of the patients were on extremely low doses. These patients also spent fewer days in the hospital compared to patients treated with the traditional paradigm. Another group conducted a study where they had very stringent criteria to use antipsychotics. Not only were they able have 37% of patients never use antipsychotics, 88% of patients were never re-hospitalized during the follow-up window of two to five years! These results are excellent, and more healthcare institutions in the US would do well to follow the example of these researchers.

As far as alternatives to antipsychotic treatment, psychosocial treatment has emerged as a valuable option [3]. One part of this treatment is family psycho-education, where a working relationship is established between the clinicians and the patient's family. This can greatly help in monitoring symptoms, and a potential relapse can be caught in its early stages. It also has the added benefit of increasing the family support for the patient. Once the family understands what is going on, they will be much better equipped to deal with any problems. This form of treatment has been shown to reduce hospital readmissions and relapses, and also decreases the stress on the family. Furthermore, it decreases the stress the patient experiences from his or her family, and that fact alone leads to better outcomes. Another important aspect of psychosocial treatment is teaching the patient how to manage his or her illness. Patients learn about schizophrenia and its treatment, so that they can take an active role in their own care. Patients are also taught how to monitor for signs of a relapse, and they are taught to create plans to prevent that from happening. Most importantly, the patients learn coping skills that can help them lower their stress and prevent the illness from reoccurring.

One such coping skill is exercise. It has a host of physical benefits, and recent research has shown it has mental health benefits for patients with schizophrenia [15]. One of the most efficient forms of exercise is high-intensity interval training (HIIT). In this design, there are alternating "work" and rest periods of short duration. During the "work" period, a participant exerts his or her full effort, in order to reach 85-95% of the maximal heart rate. Researchers in Taiwan conducted a study where they assigned 20 schizophrenic patients to complete an 8-week HIIT program. At the end of the study, patients had significantly decreased symptoms of schizophrenia as shown by their results on the Positive and Negative Syndrome Scale (PANSS). Additionally, patients had significantly decreased anxiety and depression, as shown by their results on the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), respectively. This shows that something as simple as exercise has clinical benefits for patients with schizophrenia.

Overall, dopamine supersensitivity is a major driver of schizophrenia. It is a major risk factor for the condition, and treatment with antipsychotics intensifies the supersensitivity. Many clinicians do not realize this, and some patients are needlessly on medication for years, simply because some doctors believe that medications are the best and only way to treat schizophrenia. The research showing the negative long-term outcomes of antipsychotic medica-

tions has been available for decades, but the prevailing paradigm of treatment has not changed to reflect this. Perhaps it is more profitable to just prescribe medications for every patient; it certainly is simpler. However, doctors owe it to their patients to find the best course of treatment to minimize harm and increase their quality of life, whether it is medication or another form of treatment. Doctors need to assess the possibility of discontinuation of medication for each patient, and they need to make sure the withdrawal process is slow, so that the patient's dopamine receptors can return to normal and new onset psychosis does not occur. Some patients without previous psychiatric history have had their lives turned upside down because of a failure in this regard, so it is very important to establish guidelines so that this does not occur.

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