Investigating the Role of Dopamine and Serotonin in Causing Hallucinations in Patients with

Author: Batool, Rida and **Co-Author:** Fleming, Leah

Abstract:
Can you imagine hearing voices in your head which become a hindrance to your day-to-day life? For patients with schizophrenia, this can be a common experience. Schizophrenia is a psychiatric illness affecting about 1% of the population with a variety of symptoms that patients can experience. One of these symptoms is hallucinations which is one of the most distressing, least understood and most complex experiences. Hallucinations are defined as a sensation that occurs without an external cause and occur in the majority of patients with schizophrenia. One of the main neurotransmitters believed to be involved in schizophrenia is dopamine, but more recent research has implicated other neurotransmitters as well. It is important to therefore understand the role of these various neurotransmitters in schizophrenia and hallucinations specifically. In this paper, we will focus on the technical, neurobiological mechanisms of hallucinations. First, we will review papers on the role of dopamine in hallucinations, then review papers on the role of serotonin, a different neurotransmitter. Specifically, we will research the role of these neurotransmitters in auditory, visual and somatosensory hallucinations. We will be including scientific literature found through Pubmed and various scientific journals in the fields of neuroscience and psychiatry. Understanding the role of these two neurotransmitters in different types of hallucinations has important implications for finding new treatments for schizophrenia and improving our knowledge about this debilitating symptom of hallucinations. There is currently no cure for schizophrenia and poor understanding of what causes hallucinations, leaving many patients to deal with symptoms alone.

Introduction

Schizophrenia is a mental illness that affects less than 1% of the global population, including approximately two million Americans. The illness has a significant influence on the patient's thoughts, moods, and behaviors. Patients would experience a variety of symptoms, including hallucinations and delusions, as well as lack of interest and social withdrawal. Hallucinations occur when you perceive things that don't come from the environment or any external stimulation. Hallucinations can be categorized as somatosensory, visual, and auditory. While there is no single definitive answer to what causes schizophrenia, scientists have researched and developed several hypotheses. Many of these hypotheses centered on the role of neurotransmitters like serotonin, glutamate, and dopamine in schizophrenia. The hypotheses we will discuss in this paper is the role of dopamine and serotonin in schizophrenia, with a particular focus on each neurotransmitters' role in hallucinations.

What role does dopamine play in the development of hallucinations in schizophrenia patients?

For the last 50 years, scientists have believed that dopamine dysregulation was the cause of symptoms in patients with schizophrenia. The evidence that has led scientists to believe this revolves around three main observations: 1) dopamine hyperactivity at D2 dopamine receptors, specifically meaning that there was excessive dopamine in the mesolimbic pathway 2) Drugs which reduce dopamine help treat symptoms and 3) Drugs which increase dopamine can induce symptoms of schizophrenia in otherwise healthy controls. Here we will outline these three lines of evidence. Many studies have supported the claim that patients with schizophrenia have an excess of dopamine in their brains; one such study measured dopaminergic neurotransmission in the striatum of patients with schizophrenia compared to healthy controls. The study's findings revealed that patients with schizophrenia had higher levels of dopamine than healthy controls (Pogarell, 2012). Another meta-analysis study that reached the same conclusion on a much larger scale compared PET imaging of 618 patients with schizophrenia to 606 healthy controls (Howes, 2012). The findings showed that patients with schizophrenia had high levels of dopamine release and excess dopamine production (Howes, 2012). The effects of excessive dopamine production are most visible in the D2 dopamine receptors. A study compared 18 patients with schizophrenia to 18 healthy controls to measure dopamine binding in the striatum at D2 receptors. Dopamine binding to D2 receptors was found to be increased in schizophrenia patients (Abi-Dargham, 2000).

According to these studies, there appears to be a pattern in dopamine levels in schizophrenia patients, as they are higher than in healthy controls. To further investigate hallucinations in schizophrenia patients, we must first determine whether there is a link between increased dopamine levels and hallucinations. Dopamine hyperactivity in the ventral striatum is thought to be responsible for paranoia, delusions, and even hallucination, according to research (Stahl,

2018). Rolland and colleagues hypothesized the same thing, claiming that positive symptoms of schizophrenia (hallucinations, paranoia, and delusions) could be caused by excessive dopamine transmission. This hypothesis was supported further by imaging techniques that confirmed the link between increased dopamine and positive symptoms (Rolland, 2014).

Methamphetamine is a drug that is said to worsen psychotic symptoms in Schizophrenia patients and cause psychotic symptoms in nonclinical people. This medication increases dopamine release in the brain while also inhibiting dopamine reuptake. Methamphetamine is well known for causing a temporary psychotic state characterized by persecutory thoughts and auditory or visual hallucinations. When patients with schizophrenia use methamphetamine, their psychotic symptoms can worsen. These symptoms were observed in a research study. 309 participants aged 16 and up were recruited and instructed to take the drug on a monthly basis. As a result, methamphetamine users who are already predisposed to psychosis, such as schizophrenia, run an especially high risk of developing psychotic symptoms. People who have schizophrenia will experience a much significant increase in psychotic symptoms than normal patients. A pattern can be observed since a drug that increases dopamine is increasing the risk of positive symptoms such as hallucinations (McKetin, 2006). It is possible to assume there is a causal relationship between increased levels of dopamine and hallucinations.

Dopamine is not found throughout the body, but it is a neurotransmitter in the brain. Dopamine may be causing hallucinations in a specific area of the brain. As previously stated, researchers have long believed that delusions, paranoia, and hallucinations are caused by dopamine hyperactivation in the mesolimbic pathway. This route links the ventral tegmental area to the ventral striatum. The hyperactivation does not appear to affect the neighboring region of the dorsal striatum on the other hand (Stahl, 2018). When studying the relationship between dopamine levels and schizophrenia, it is preferable to focus on these specific regions rather than the entire brain. As such, many research studies to find a treatment for patients with schizophrenia have focused on these specific areas.

These hypotheses and studies have been a major assistance for creating drugs that help to reduce the negative and positive symptoms in patients with schizophrenia. Many of the drugs that were created to treat schizophrenia seem to target dopamine specifically. However a significant proportion of people with schizophrenia and other psychotic disorders do not respond well to antipsychotic medication right away. Poor therapeutic response is linked to poorer functional outcomes, higher healthcare costs, and an increased risk of suicide. Understanding the neurobiological basis of treatment response and how these drugs affect different symptoms is critical for developing more effective pharmaceutical treatments (Jauhar, 2019). One such study that aimed to answer this question was named the EUFEST study, which included 498 patients with schizophrenia. Those patients randomly received various antipsychotics that work to block dopamine. The purpose of the study was to observe the effects of these antipsychotics

in reducing hallucinations. However, the results showed no significant difference between the antipsychotics in reducing hallucinations. Though most of the drugs had very little reduction in hallucinations. Therefore it may not reduce the symptoms significantly, but could have a very minor effect (Sommer, 2019). This might assist in the development of a stronger drug that can actually prevent these positive symptoms. Another drug that increases the levels of dopamine was used to conduct a research study. The Study measured amphetamine-induced dopamine release in the striatum of fifteen patients with schizophrenia and fifteen healthy controls using a single photon emission computerized tomography method. The reduction in dopamine D2 receptor availability caused by amphetamine was used to estimate amphetamine-induced dopamine release. The results showed the emergence or worsening of positive psychotic symptoms in the schizophrenic group that had taken the amphetamine-induced drug. This finding suggests that in this experiment, psychotic symptoms elicited in schizophrenic patients are associated with excessive stimulation of dopaminergic transmission. This finding is consistent with abnormal dopaminergic neuron responsiveness in schizophrenia (Laruelle, 1996). Amphetamine, as mentioned before, increases dopamine in the Striatum. Researchers used that to conduct a study and experiment this hypothesis of increased dopamine levels causing positive symptoms in Schizophrenia. Another study which sought to better understand the mechanism of treatments for schizophrenia conducted brain imaging on patients undergoing treatment. Though there are many limitations and drawbacks when experimenting new treatments, it allows researchers to expand their knowledge for future studies. One study gave 40 volunteers (26 patients with first-episode psychosis and 14 controls) an 18F-DOPA Positron Emission Tomography scan to measure DSC (Jauhar, 2019). This was done before the volunteers were given the antipsychotic treatments. Clinical assessments Global Assessment of Functioning were performed at start point and after 4 weeks of antipsychotic treatment. The conclusion the researchers came to was that antipsychotic treatment response in psychosis is related to pre-existing presynaptic dopamine function. Researchers came to a conclusion that in addition to clinical variables, neuroimaging measures could be used to help identify patients with psychosis in order to predict future antipsychotic response and non-response (Jauhar, 2019). This study allowed researchers to understand the reason for various responses to antipsychotic treatments and gave future reference to what instruments and technology could be used in further research. Overall, based on the evidence presented, dopamine does in fact play a major role in Schizophrenia, specifically causing hallucinations.

What role does Serotonin play in the development of hallucinations in schizophrenia patients?

Since the early 20th century, when it was discovered that serotonin could contract smooth muscle and was later thought to be a target for antihypertensive drugs, it has been linked to many areas of pathophysiology and pharmacology. Serotonin is a neurotransmitter with a molecular structure of 5-hydroxytryptamine (5-HT). A wide range of processes, including

neuronal growth, appetite, and mood, appear to be significantly influenced by serotonin. It is not unexpected that 5-HT has also been associated with a variety of psychiatric diseases, including eating disorders, suicide, and most importantly schizophrenia, given its role in higher-order human processes (Breier, 1994). Prior to the discovery of the link between serotonin and schizophrenia, experts thought that the sole neurotransmitter involved in the positive symptoms of schizophrenia was dopamine. Since the discovery of serotonin, the hypotheses have evolved, and now a large amount of research is focused on serotonin as a significant contributor to the positive symptoms of schizophrenia. Many studies have been conducted to determine the effects of serotonin in patients with schizophrenia. However, there have been mixed results about serotonin levels in patients with schizophrenia. Some studies have shown an increase in serotonin levels, while some studies have shown no difference in serotonin levels in patients with schizophrenia (Cumming, 2021). One paper was studying the serotonin transporter levels in the brainstem (a region where serotonin is produced) in patients with schizophrenia compared to healthy controls. The results of the study concluded that there was no difference in the levels of serotonin transporters in patients (Laruelle, 2000). Yet other studies show increased serotonin levels in patients with schizophrenia compared to controls. These different conclusions might relate to which brain region is being studied and which marker of serotonin is being measured. For instance, it's been shown that different types of serotonin receptors have different levels in different brain regions of the limbic system (Joyce, 1993). One such brain region that has shown increased levels of serotonin is the prefrontal cortex. Specifically, there was an increase in the serotonin 2A receptors (Muguruza, 2013). Genetic studies have also revealed changes in genes of serotonin in patients with schizophrenia. Genes involved include synthesis, transport, receptors, reuptake, and breakdown of serotonin, and they have all been shown to be related to schizophrenia (Hrovatin, 2020).

Although many studies show an increase in serotonin levels in patients with schizophrenia, many other studies indicate a decrease in serotonin levels. This claim was supported by a post-mortem study in which the brain tissue of schizophrenia patients was analyzed. In the cortical regions of the brain, primarily the frontal cortex, eleven out of the sixteen studies showed a reduction in 5-HT2A receptor expression (Ebdrup, 2011). PET studies have also been carried out, though not as frequently as post-mortem investigations. Five PET studies on schizophrenia patients were conducted, and three of them revealed no appreciable difference in 5-HT2A levels between the patients and controls. However, two of the studies revealed a reduction in the density of frontal 5-HT2A receptors (Ebdrup, 2011). Six patients with schizophrenia participated in a second PET study, which revealed a reduction in 5-HT2A in the le lateral frontal cortex (Ebdrup, 2011). 30 schizophrenic patients participated in one of the largest PET studies, and the findings revealed a general decline in 5-HT2A receptor binding in the cortex, primarily in the frontal cortex (Ebdrup, 2011).

The brain has many parts to it with very unique functions, but not all contribute to the release of serotonin in the brain. To understand the relationship between serotonin and schizophrenia, researchers have to first understand where in the brain serotonin is having the most effect. In order to better understand the changes in serotonin levels, researchers collected data from certain limbic regions of the brain. They found that specific limbic regions such the hippocampus, accumbens, and posterior cingulate have higher concentrations of 5-HT2A and 5-HT2A receptors in patients with schizophrenia compared to controls (Breier, 1994). These are some of the few brain regions that are said to release serotonin in the brain. However, another part of the brain that is more widely observed when understanding serotonin is the frontal cortex. The frontal cortex is crucial for perception and cognition, and it has more recently been linked to schizophrenia and other psychotic diseases (Muguruza, 2013). Many studies including post-mortem and PET studies generally concluded that there was a decrease in serotonin levels in the cortex, but the majority of them showed that the frontal cortex had the greatest decrease compared to the other regions. (Ebdrup, 2011). The 5-HT2A receptors have shown to be found in the prefrontal cortex of the brain. 5-HT2A receptors are involved in neuronal circuitry modulation in both the medial prefrontal cortex and the hippocampus. 5-HT2A receptors are expressed postsynaptically on pyramidal cells and local circuit neurons in the prefrontal cortex (Richtand, 2008). Other brain regions may yet be discovered, but these are the ones that have received the most attention in research. Although there are mixed results about changes in serotonin related to schizophrenia, overall it appears that this neurotransmitter system is disrupted.

A symptom present in patients in schizophrenia that has been connected to serotonin is hallucinations. One way in which researchers can test the relationship between serotonin and hallucinations is to give drugs that either increase or decrease serotonin and measure the outcome. One such drug that was used in this type of study is lysergic acid diethylamide (LSD). LSD is a drug that binds to a specific serotonin (5HT) receptor (2A receptor) and activates it to increase serotonin transmission; psilocybin and other serotonergic psychedelics similarly bind to 5HT-2A receptors and increase serotonin transmission. After many years with limited studies due to legal regulations on this class of drugs, LSD based research and practice has recently begun once more. After administering a certain dose of LSD to healthy controls, LSD created clear changes in waking consciousness that persisted over 12 hours. Visual hallucinations, audiovisual synesthesia, positively reported derealization and depersonalization events were the main LSD side effects (Geyer, 2015). There is a significant degree of overlap between hallucinogen-induced psychosis and the early phases of psychosis, such as hallucinations, conceptual disarray, and strange thoughts, according to studies comparing hallucinogen-induced psychotic states with psychosis (Gregorio, 2016). One study used Minnesota Multiphasic Personality Inventory (MMPI) to examine 10 LSD users and 46 non-users. They discovered that LSD users had a considerably higher incidence of psychosis than non-users. According to the MMPI scale, LSD users tend to be isolated, have emotional

disturbances, high levels of anxiety, despair, hallucinations, paranoia, and suicidal thoughts (Gregorio, 2016). Changes in fundamental visual processing are another LSD effect that may exacerbate cognitive bizarreness and contribute to the hallucinogenic effects of this drug. This is corroborated by a neuroimaging study , which demonstrated a strong correlation between LSD-induced primary visual cortex activation and both simple and complicated hallucinations (Kraehenmann, 2017). Another drug which similarly increases serotonin 2A activity, also causes psychosis-like symptoms, and changes in visual perceptions is psilocybin. Administration of a serotonin 2A antagonist blocks the psychotic symptoms caused by psilocybin, proving the involvement of this receptor in hallucinations (Vollenweider, 1998). Overall these studies demonstrate that drugs which increase serotonin in the brain, such as LSD or psilocybin, can cause people who do not normally hallucinate to experience hallucinations. This creates a causal link between serotonin and hallucinations.

These hypotheses and studies on the role of serotonin in hallucinations and other symptoms of schizophrenia have greatly aided in the development of novel drugs that help to reduce both negative and positive symptoms in patients with schizophrenia. Atypical antipsychotics, the most commonly used class of drugs to treat schizophrenia, act on two serotonin receptors: 5HT2A and 5HT2C receptors (specifically they block the 5HT2A receptors). These atypical antipsychotics act on both dopamine and serotonin, but their effectiveness strongly suggests that serotonin plays a role in the treatment of psychosis (Richtand, 2008). Various studies are currently being conducted to investigate novel antipsychotic drugs that may target serotonin and their effect on symptoms. A PET study using quetiapine in first-episode schizophrenia patients who had previously been antipsychotic-naive found that blocking 5-HT2A receptors was associated with a reduction in positive symptoms (Ebdrup, 2011). This 5-HT2A-related clinical effect appeared to be most pronounced at a dose of 400 mg quetiapine. The researchers came to the conclusion that blocking 5-HT2A receptors in combination with a small D2 blockade can actually be most beneficial in reducing positive symptoms. (Ebdrup, 2011). All of the medications developed for the treatment of psychosis rely on treating patients already experiencing severe deficits , and there is no reason to believe that these treatments would be the safest and most effective in first-episode psychosis as a preventive treatment. Evidence suggests that selective serotonin reuptake inhibitors, serotonin 5-HT2A and dopamine D3 receptor antagonists, mood-stabilizing medications, GABAergic, glutamatergic, and neuroprotective compounds may be as effective as first-episode psychosis prevention drugs (Richtand, 2008). A study by Cornblatt, (2007) showed that antidepressants were more effective than antipsychotics at preventing a person who is identified to be at high risk (e.g. showing early signs of the disease) from developing schizophrenia. This is relevant to the 5HT-2A receptor because most of the antidepressants used were selective serotonin reuptake inhibitors, meaning they act selectively on the serotonin system. The majority of medications used in the antidepressant treatment group included serotonin (5-HT) reuptake inhibition as a mechanism of

action, they do suggest the deterministic possibility that 5-HT reuptake inhibition may be an effective medication development target for psychosis prevention (Richtand, 2008).

Conclusion

Although it is difficult to say which chemical has a greater effect than the other, it is clear that both dopamine and serotonin play a significant role in schizophrenia. Both neurotransmitters appear to be linked in some way, and in some cases they appear to act in tandem. However, as this research paper discusses, there is more evidence indicating a greater role of dopamine in schizophrenia than serotonin. This is partly because the role of serotonin in schizophrenia was not studied extensively until recently.

Overall, the evidence shows that dopamine plays a significant role in the development of hallucinations in patients with schizophrenia, as excess dopamine increases the risk of developing psychotic symptoms such as schizophrenia (Stahl, 2018). As a result, scientists have hypothesized that patients' psychotic symptoms are caused by excessive dopamine release in the ventral striatum of the brain. In comparison, serotonin research points to the possibility that an increase in serotonin may also be the cause of specifically hallucinations in patients. This hypothesis was derived from participants being given LSD, a drug which activates serotonin receptors in the brain, and experiencing hallucinations (Geyer, 2015). Other research also indicated that a decrease in serotonin levels can somewhat reduce positive symptoms (Ebdrup, 2011). Unfortunately, research on the role of serotonin in schizophrenia has been more scarce and mixed as compared to dopamine. But in general, it appears that there are differences in the serotonin system in patients with schizophrenia.

Furthermore, most treatments for schizophrenia have used a combination of neurotransmitters. Atypical antipsychotics, the most popular treatment for schizophrenia, acts on both dopamine and serotonin receptors to alleviate symptoms. Additionally, drugs which act on both dopamine and serotonin can cause psychotic symptoms, including hallucinations and altered perception. Amphetamine, for example, increased the amount of dopamine released, which worsened the positive symptoms in patients with schizophrenia (Laruelle, 1996). Similarly, drugs that increase serotonin, such as LSD and psilocybin, were given to patients and showed an increase in psychotic symptoms (Geyer, 2015). According to some research, dopamine and serotonin may play more direct roles at different stages of schizophrenia (When symptoms first emerge versus over the long term) (Ebdrup, 2011).

The conclusion that we have reached in this research paper is that dopamine and serotonin both play a significant role in causing hallucinations in schizophrenia, as well as in treating these symptoms. It is difficult to say which neurotransmitter causes schizophrenia more than the other because both have an impact on this psychological disorder in distinct manners. Future

research could shed more light on this debate by examining serotonin and dopamine levels in the same patient rather than a different patient. Future research should concentrate on developing a technology that can detect dopamine and serotonin levels accurately and monitor any abnormalities. This will enable researchers to gain a better understanding of their roles in causing hallucinations in schizophrenia patients.

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