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Stress, Dopamine and the Development of Schizophrenia

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Abstract: Dopaminergic dysregulation and dysfunction have long been seen as the key factors of the onset of psychosis. The dopamine hypothesis postulates hyperactivity of subcortical dopamine release and hypoactivity of cortical dopamine transmission in schizophrenia, indicating the relationship between irregular dopamine activity and the development of positive and negative symptoms of schizophrenia. Meanwhile, psychological stressors affect the brain in multiple ways, including changing the structure of neurons and causing malfunction of the dopamine system. These changes are also critical in causing psychotic experiences. Despite there are abundant studies and findings investigating either the relationship between dopamine and schizophrenia, or the relationship between schizophrenia and stress, few of them have put these three concepts together in discussion. This paper aims at investigating how abnormal dopamine functions, stress and schizophrenia are related to each other, which helps generate a deeper and clearer understanding of the disease from a broader view. The relationship between inappropriate dopamine release and the pathophysiology of schizophrenia is discussed, particularly talks about the dopamine transmission in striatal and cortical regions of the brain, it proceeds into an investigation of the association between stress and schizophrenia from both physiological and sociological scopes, and then summarizes the current ways of treating schizophrenia provided along with the future prospect in developing treatments for this disorder.

Keywords: stress, dopamine, schizophrenia, dopaminergic dysregulation, social stressors

1. Introduction

Dopamine acts as the key neurotransmitter in neural activities that are associated with reward processing, reinforcement and habit formation [1]. There is a large amount of evidence indicating the association between schizophrenia and dopaminergic dysregulation. In studies of dopamine-releasing drugs, after taking drugs like amphetamines, patients in the experimental group experience worsening symptoms while healthy participants start to have psychotic symptoms [2]. Based on molecular imaging studies, stronger striatal dopamine synthesis capacity is present in patients with schizophrenia while the higher amount of dopamine release after amphetamine application is closely related to severe cases of experiencing psychotic symptoms of schizophrenia [2]. On the other hand, through striatal dopamine levels depletion or dopamine receptor blockade, patients experience lower levels of psychotic symptoms [2]. This evidence suggests that dysregulation of the dopamine system could be a final common pathway to psychosis, which also implies that schizophrenia can possibly

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be managed by blocking dopamine receptors and reducing striatal dopamine levels [2]. Overall, dopaminergic dysregulation is central to varied models of the pathophysiology of schizophrenia [1].

1.1. Schizophrenia and Striatal Dopamine Function

The striatum is a subcortical structure that consists of two parts: the dorsal striatum (i.e. caudate, putamen) and the ventral striatum (i.e. nucleus accumbens) [3]. It is located in the midbrain and is in charge of the modulation of neuronal input to the basal ganglia. It is also involved in motor behaviour regulation as well as rewarding and aversive stimuli response [3]. Early postmortem studies have shown that, within the patients with schizophrenia, there was a higher level of dopamine concentrations in the nucleus accumbens (NAcc), while the concentrations of dopamine also increased in the dorsal striatum [4]. Furthermore, both dopamine receptor density and the activity of tyrosine hydroxylase, which is a rate-limiting enzyme in dopamine synthesis, increased throughout the striatum. There was counter-evidence found in recent studies which demonstrated few differences between patients and the control group regarding dopaminergic terminal density or tyrosine hydroxylase levels in the NAcc [4]. Results from these postmortem studies, however, are limited in making inferences about the association between schizophrenia and striatal dopamine function in the sense of antipsychotic drug consumption, which could lead to upregulation of dopamine receptors, as well as affecting presynaptic dopamine function in the patients [4]. Moreover, death is a critical factor that influences dopamine and its metabolites in postmortem studies, by which the outcomes are limited in showing striatal dopamine function in living patients with schizophrenia [4].

Later, due to the development of new techniques, details of the relationship between striatal dopamine signaling and schizophrenia were further revealed. Optogenetics, for instance, is a biological technique that is often used in the investigation of neuronal activity. By using light to control genetically modified neurons that express light-sensitive ion channels, optogenetics enabled selective targeting of striatal dopamine neurons, allowing studies of these neurons to be at a synaptic level, and thus enabling functional connectivity analysis of the targeted neurons [3]. More recently, studies have shown that through optogenetic stimulation of mesostriatal dopamine neurons, induced elevated levels of striatal dopamine led to hallucination-like perception [5]. These study results reveal a causal relationship between striatal dopamine circuits and hallucination-like percepts [5]. Since hallucination is a well-known symptom of schizophrenia, these findings also demonstrate that the increase in striatal dopamine levels is causally related to the development of schizophrenia.

Here is another example of the role of new techniques in studying the relationship between striatal dopamine dysregulation and schizophrenia: positron emission tomography (PET) has enabled measuring the uptake of dopamine precursor L-dihydroxyphenylalanine (L-DOPA) and its conversion in dopamine neurons through radiolabelling this amino acid; also, the baseline levels of dopamine and the amount of dopamine release can be determined through imaging the competition between endogenous dopamine and radioligands specific to postsynaptic dopamine receptors [4]. By using higher-resolution PET scanners, studies have reported that, contrary to the influential mesolimbic hypothesis of schizophrenia, the greatest dopaminergic aberrations were found in the associative region of the striatum rather than the mesolimbic dopamine pathway [4]. Furthermore, in the investigation of presynaptic dopamine function, research has shown that individuals who were found the greatest abnormality in the associative striatum were also at clinically high risk (CHR) of psychosis [4]. With a progressive increase in dopamine synthesis capacity in the dorsal, predominantly sensorimotor, striatum, CHR converts into the onset of psychosis [4].

This aberrant dopamine functioning in the striatum can lead to schizophrenia in multiple ways. For instance, studies have revealed the involvement of mesostriatal dopamine signaling in addressing the salience of external or internal stimuli; having excessive dopamine transmission in the striatal region, it draws temporal association between the stimuli and striatal signaling, which attaches

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unnecessary significance to the environmental stimuli in cognition [4]. Meanwhile, since dopaminergic activity in the regions of the dorsal striatum is driven by threat-related information, the consequential delusions are often persecutory in nature [4].

It is worth noticing that a stimulus maintains the ability to evoke dopaminergic activity once it has been highlighted by aberrant dopamine signaling. This means that the association drawn between the environmental stimulus and dopaminergic activity continues to exist over time once the stimulus is paired with dopaminergic activity, which suggests that in psychosis, the highlighted stimulus is likely to lead to delusions even after the system returns to normal function [4].

1.2. Schizophrenia and Cortical Dopamine Function

In explaining the phenomenological aspects of schizophrenia, the dopamine hypothesis of schizophrenia postulates that while positive symptoms of schizophrenia are driven by hyperactivity of dopamine transmission in subcortical and limbic regions of the brain, negative and cognitive symptoms of the disorder can be attributed to hypoactivity of dopamine transmission in the prefrontal cortex [6-7]. Recently, research done by Frankle, W.G. et al. [6] reported blunted levels of amphetamine-induced dopamine release in some cortical regions of subjects with schizophrenia, including the hippocampus, parahippocampal gyrus, entorhinal cortex, temporal cortex, medial prefrontal lobe cortex, parietal cortex, and, at a trend level, the dorsolateral prefrontal cortex (DLPFC) [6]. The research results correspond to two prior studies examining cortical dopamine transmission in schizophrenia. Slifstein et al. [8] reported lower dopamine release specifically in the DLPFC of the subjects with schizophrenia, while Rao et al. [9] found a significant decrease in dopamine release in the anterior cingulate cortex and a trend-level reduced dopamine release relative to the control subjects. Compared to the other two studies, Frankle, W.G. et al. [6] demonstrated widespread impairments of cortical domaine transmission in schizophrenia.

Furthermore, studies have shown that, instead of being independent, the impairments in cortical and striatal dopamine transmission are more likely to be inversely correlated [6]. This conceptualization is based on evidence from preclinical studies. For instance, dopamine depletion in the medial prefrontal cortex of rodents leads to an increase in striatal dopamine levels, which is presumably due to the removal of the prefrontal cortex's inhibitory effect on midbrain dopamine neurotransmission towards the striatum by causing lesions to the rodents' medial prefrontal cortex. Meanwhile, dopamine-depleting lesions in the prefrontal or orbitofrontal cortices of primates also result in increased dopamine levels in the caudate [6].

There are theories suggesting that the alterations in dopamine levels in the striatal regions are likely to be primary in schizophrenia development, which then affect dopamine release in cortical regions of the brain. Being a structure within the associative striatum, which is the striatal region most interconnected with the DLPFC, the dorsal caudate is involved in working memory as well as other cognitive functions [6]. Impairments in frontostriatal functional connectivity are found in subjects with schizophrenia, which are associated with impaired working memory [6]. A recent study has found disordered frontostriatal connectivity to be most prominent in the caudate [6]. While the degree of connectivity damage is correlated with positive symptoms and lower density of cortical D2/3 receptors, no correlation has been found between the level of impaired connectivity and amphetamine-induced cortical dopamine release [6]. This finding seems to suggest that the disrupted connectivity leads to damage in higher-order cognition possibly through dopaminergic mechanism [6]. Further research is required to examine this issue.

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2. Stress and Schizophrenia

Late studies show that the disruption of upstream circuits, through which afferent control of midbrain dopamine neurons has interfered, is directly associated with the malfunction of the dopamine system, while the presence of stress profoundly drives such disruption of the regulatory circuit [1]. Both chronic social stressors and early-life stressors increase the risk of developing schizophrenia in the way that stress changes the physiological structure of the brain and interferes with normal neural activities. Psychosocial stressors, such as racial minority status, childhood adversity and urban environment, sensitize the subcortical dopamine system, resulting in cortical deficits and an increase in the response to later triggers [1]. The presence of cortical deficits means that the regulatory control is impaired; along with the sensitized response to stimuli, it means that when patients with chronic stress face subsequent triggers, they experience a greater amount of striatal dopamine release while not being able to regulate it appropriately. This leads to abnormal salience to stimuli, which then leads to the development of psychotic symptoms [1]. Meanwhile, psychosis itself is stressful, thus patients who have already developed relative symptoms enter a vicious cycle, in which they continue to receive negative feedback that further disrupts the system [1].

Physiologically speaking, chronic stress in adults leads to dendritic retraction and spine loss in multiple brain regions, among which is the prefrontal cortex (PFC). The PFC plays a major role in higher-order cognitive tasks, due to which it is more sensitive to stress than other brain regions. Dendritic retraction takes place in the PFC even after it has been exposed to aversive stimuli for a short period of time. Moreover, the PFC receives dopamine release from the ventral segmental area (VTA) which increases its neural activities in the presence of stressors [10]. This results in higher levels of dopamine reception in the PFC under stressful circumstances, leading to stress-induced PFC dysfunction. Besides, studies have shown that early-life stress (ELS) increases dendritic spine density and excitatory synapse density in the dorsal PFC, while it also increases the firing of PFC-projecting mesocortical DA neurons in the VTA [10]. These alterations, both those that are caused by chronic stress in adults and those that are caused by ELS, are long-lasting, meaning that individuals who have been constantly exposed to aversive stimuli are likely to be permanently vulnerable to dopaminergic dysregulation and PFC dysfunction [10]. As mentioned previously, both dopaminergic dysregulation and PFC dysfunction are factors directly associated with the development of schizophrenia.

Sociologically speaking, social stressors, such as low social status and repeated humiliation, are associated with the development of psychotic-like experiences [11]. The word “status” used in this context refers to the voluntarily given respect, admiration and deference to an individual by other people, which depends on that individual’s general value perceived by others. The desire for status has been broadly seen as an essential motive in driving human actions, while an inadequacy in status is correlated with the development of many diseases [11]. Low status negatively affects health not only because of its association with common risk factors for diseases, such as smoking, obesity, stress and lack of exercise. It is also pathologic in the sense of its positive correlation with an insufficiency in social participation and autonomy that is associated with the concomitant threat to low self-esteem [11]. Monsonet et al. [12] reported that low self-esteem, anxiety and sadness are critical factors in the mediation of the pathway from stress to psychotic-like experiences as well as paranoia in daily life.

Meanwhile, results from animal studies have shown that low social status is a factor in the progressive increase in dopamine response [11]. By devising a large living environment for inbred mice, in which certain members were subjected to social defeat, the study revealed that the differences in subject behaviours were reflected by diverse dopamine neuron firing properties in the midbrain. Because genetic diversity was little, the results suggest a potential correlation between low social status and dopaminergic dysregulation. Besides low status and humiliation, aversive early-life experiences are also a factor in psychosis development. Negative experiences in the early time of life

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may lead to cognitive biases. Experiences such as bullying and child abuse can lead to a tendency to view negative events as the result of the hostile acts of others. These cognitive biases are more common in people who are at risk of developing schizophrenia [1].

3. Treatments

In the current drug market, all pharmacological treatments for schizophrenia are dopamine D2-receptor blockers. By blocking these dopamine receptors, the drug helps inhibit the consequences of dysregulated dopamine transmission [1].

In more recent studies, in the context of treating cognitive impairments through reversing dopaminergic dysfunctions, the dopamine D3 receptor (D3R), a member of the D2-like family, has been a promising molecular target in pro-cognitive therapy development. Findings have shown that D3R-mediated signaling is crucial in expressing cognitive functions, while the disruptions in D3R-mediated signaling are key factors leading to cognitive dysfunctions. Based on its cortical localization, the findings suggest that D3R plays an important role in PFC-related cognitive processes. In later preclinical studies, D3R knockout subjects demonstrated enhanced high-order cognitive functions such as attentional set-shifting and working memory [13]. Over the years, the results from studies of D3R have been implemented in therapeutic applications, in which D3R antagonists, such as S33084, S33138 and F17464, were developed as experimental drugs for cognition enhancement. Among all these D3R-targeted drugs, F17464, has reached the clinical phase as potential antipsychotic, and demonstrated efficacy in treating positive and negative symptoms of schizophrenia as well as cognitive dysfunctions, without causing severe side effects [13-15].

Besides pharmacological ways of treating schizophrenia, there are also social methods that can be applied to schizophrenia prevention and treatment. The previous discussion reveals a clear relationship between stress and the development of schizophrenia. By enhancing the welfare systems, especially for children and socially marginal groups, the decrease of psychosocial stressors can help protect the regulatory circuits of dopamine and the PFC, through which they help protect the vulnerable population from the risk of developing schizophrenia.

4. Conclusion

The development of schizophrenia seems to be directly associated with dysregulation of the dopamine system in both cortical and striatal brain regions, while the impairments in cortical and striatal dopamine release are inversely correlated with each other: by reducing the cortical dopamine levels, an increase in the striatal dopamine transmission was observed. These findings correspond to the dopamine hypotheses of schizophrenia.

In addition, stress is a critical factor in disrupting the regulatory circuits of dopamine. From the sociological point of view, people who experience chronic stress are at greater risk of developing schizophrenia. Psychosocial stressors, such as low social status and repeated humiliation, are associated with a lack of social participation and a lack of autonomy, which can lead to paranoia and psychotic-like experiences by threatening one's self-esteem. Meanwhile, low status is also associated with dopaminergic dysregulation, yet due to the fact that not all individuals with low social status experience schizophrenia, the relationship between this social stressor and the development of schizophrenia needs to be investigated through further studies. For treatments, D2-receptor blockers are the only current pharmacological method in treating schizophrenia, among which D3R antagonists are promising drugs for schizophrenia treatment. For future therapeutic applications, besides the pharmacological aspect of treatment development, the sociological aspect should also be taken into consideration as psychosocial stressors are key factors in causing irregular dopamine transmission as well as deficits in cognition. The improvement of the welfare system can also help reduce the amount

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of stress people are exposed to, by which the vulnerable population can be protected from the risk of schizophrenia development.

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