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Florence Nightingale

Review

Dopamine dynamics in autism: Unraveling the neurochemical puzzle

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ABSTRACT

Although the etiology of autism is not yet clearly known, it is an executive dysfunction associated with symptoms that reduce the quality of life, such as inadequate social skills, difficulties with speech and non-verbal communication (cognitive impairment), intellectual disabilities, and restricted and repetitive behaviors. Although many factors such as genetic, environmental, and autoimmune factors are included in the etiology of autism, the uncertainty on this issue still continues. However, it is also reported that individuals with autism have dopamine-based abnormalities in their prefrontal systems. Many data have shown that the prefrontal cortex (PFC) is one of the important areas contributing to executive function. Alongside the central claim of the executive dysfunction theory, there is evidence that the root cause of many autistic behaviors may be due to dopaminergic abnormalities in the PFC region of the brain. Although significant progress has been made in autism research in line with this hypothesis, there is no consensus on the basis of the neural disorder. This hypothesis of executive dysfunction suggests that it may underlie the significant cognitive performance impairments seen in autism due to the unregulated development of the PFC. Likewise, detailed analyses show that not all forms of execution are commonly disrupted. Indeed, the part of the executive dysfunction observed in people with autism that raises questions is the impairment of cognitive control while basic cognitive function remains intact. Cognitive control is the ability to perform a given response in a distracting or more automatic situation. Cognitive flexibility is the ability to adjust cognitive control fluently with changing conditions. The pathogenesis of autism has been linked to neurological and environmental factors that alter physiological processes during development. Here, research highlighting the mechanisms of dopaminergic receptors on neurodevelopmental disorders is reviewed. Therefore, this review also suggests that improving dopamine secretion may be an important therapeutic strategy in the management of autism.

Keywords: Autism spectrum disorder, dopaminergic receptors, neurodevelopmental disorder, prefrontal cortex.

A diverse range of neurodevelopmental disorders known as autism spectrum disorder (ASD) are characterized by chronic difficulties in social interaction and communication as well as constrained patterns of behavior, interest, and activity.[1-3] The pathophysiology of ASD is largely unknown, despite the many theories that have been put out. This is due to the high heterogeneity of the spectrum, which ranges from social to non-social behavioral aberrations.[4] According to research, ASD and other neuropsychiatric illnesses with similar behavioral traits, such as schizophrenia, may be related to dopaminergic dysfunctions.[5-7] Indeed, a detailed study by Dichter et al.[8] put forward the idea that dopamine imbalances in specific brain regions may lead to autistic-like behaviors. However, existing research has not been sufficient to clarify the role of dopamine signaling abnormalities in triggering the behavioral features of ASD.[9,10] Therefore, the present study was planned to review the recent research on a dopamine hypothesis for ASD and to determine the current level of knowledge despite the extensive research on this topic.

In this review article, the Medline/PubMed database was searched for systematic reviews and original studies with the keywords "Autism-dopamine hypothesis" and "Dopamine antagonists" between 1995 and 2022 that were published in English. Due to its greater breadth and access to more than 25 million pieces of biological literature, the PubMed/Medline database was chosen. In the beginning, the hypotheses proposed in light of the findings of

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the pertinent studies located in the literature searches were established in various stages. First, how particular dopaminergic dysfunctions could result in behaviors resembling those of autism, Second, an extensive examination of the primary hypothesis' predictions, Third, suggestions for how to put the theory to the test. The limitations of the hypothesis are the final step. We believe it will be feasible to determine if there is a problem in this way.

DOPAMINERGIC DYSFUNCTION ASSOCIATION WITH AUTISTIC-LIKE BEHAVIOR

The key traits of people with autism, according to studies, include social deficiencies and stereotyped behaviors.[11,12] It is believed that disrupted midbrain dopaminergic transmission is the root of these traits.[13] Two divisions of the midbrain dopaminergic neurons, the substantia nigra and ventral tegmental region, are crucial in the control of the functions that are frequently compromised by ASD. These two neuronal clusters function as two ubiquitous modulatory circuits that link diverse regions of the brain via lengthy paths. These neural ensembles can regulate sizable groups of postsynaptic neurons and have a significant behavioral impact. The prefrontal cortex (PFC) and the ventral nucleus accumbens receive projections from neurons in the ventral tegmental region first. Second, the substantia nigra projects neurons to the dorsal striatum, establishing the nigrostriatal (NS) circuit, which regulates the motor components of goal-directed behavior to create the right actions to get a certain result. In light of these, it has been hypothesized that aberrant dopamine signaling in these brain regions is what causes the core characteristics of autism.[14-17] First off, the social difficulties seen in ASD may be a result of a malfunctioning mesocorticolimbic (MCL) circuit. An MCL circuit malfunction may result in altered reward representation and decreased drive to pursue rewarding events due to its role in reward and motivation.[18] Autistic brains may fail to recognize social connections as rewarding if these changes are connected to social behavior, which would further decrease the drive to seek out social interactions and improve social skills. The social motivation theory of ASD, which holds that autistic individuals are an extreme example of low social drive that impacts social cognition and ultimately results in social deficits, expresses this point of view. Numerous studies back up this idea.[19-22] First, MCL dopaminergic circuit signaling alterations in autistic patients include decreased PFC dopamine release and decreased nucleus accumbens neuronal responsiveness.[23] Accordingly, research demonstrates that both social and non-social rewards are affected by the general hypoactivation of the reward system that characterizes ASD.[24-28] Oxytocin may play a facilitative role in MCL dopaminergic signaling as evidenced by the decreased mesolimbic activation was seen in individuals who have the oxytocin receptor gene polymorphism linked to ASD.[29] The alleviation of social deficits brought on by intranasal oxytocin delivery raises the possibility that problems in mesolimbic dopamine signaling are fundamental to the social characteristics of ASD.[30] Last but not least, it has been demonstrated that decreased mesolimbic dopaminergic signaling modifies some reward-related behaviors, including effort-based decision-making for rewards, in autistic people.[31] All of these investigations suggest that autistic individuals exhibit general MCL circuit malfunction, which leads to changes in reward-related behaviors. Thus, they could be the initial steps in a disordered chain of events that eventually results in the social abnormalities seen in ASD. Furthermore, a malfunction in the NS pathway, which has been demonstrated to mediate stereotyped behaviors, may be the cause of the stereotyped behaviors seen in autistic people.[32,33] Due to the NS route's crucial involvement in regulating goal-directed motor behaviors, failure in this pathway may result in autistic-like behaviors by trapping a person in cycles of repetitive, stereotyped behaviors.[33] A D3 dopamine receptor gene polymorphism has been linked to increased striatal volume and stereotypic behavior in autistic people. Additionally, frequent mutations in the genes encoding the dopamine transporter and the dopamine D4 receptor have been linked to repeated behaviors in kids with ASD.[34] All of these studies point to the NS pathway's dopaminergic malfunction as a key factor in the development of stereotypical behavior like that of autistic individuals. According to this dopamine theory, defects in dopamine signaling in the diffuse dopaminergic modulatory networks of the midbrain, which cause social deficits and stereotyped behaviors in ASD, serve as a link

between neurobiology and behavior, as shown in Figure 1.[35]

This viewpoint offers two fundamental predictions.

- The first is that autism-like behaviors, regardless of diagnosis (i.e., in non-autistic participants), are linked to dopaminergic dysfunctions in the same brain regions, and
- The second is that giving dopamine modulators to autistic patients improves their behavior.

ANTAGONISTS TO DOPAMINE

Models of dopaminergic pathway hyper- or hypoactivity in relation to dopamine imbalances in autistic people have been put up by certain writers.[36] No consensus that is independent of these models has been formed up until this point. Schizophrenia is believed to originate from the interaction of subcortical dopamine excess and cortical dopamine deficiency, and shares behavioral traits with ASD. Given that schizophrenia and ASD have similar behavioral traits, persons with autism may also experience a related pathological mechanism.[37] Unfortunately, there is currently insufficient evidence and further research is needed to develop a reliable dopaminergic model of ASD. It's significant since dopamine antagonists have been seen to improve basic autistic characteristics.[38] Dopamine modulators may enhance both social and non-social behavior if dopaminergic dysfunctions are the cause of autistic-like behaviors.[39-42] Due to its positive impact on behavior, blocking dopamine neurotransmission could also be a significant therapeutic approach.[43-46] The evidence, however contradictory, points to generalized dopaminergic hypoactivity in autistic people.[47] The contradictory data made it necessary to conduct additional research to identify the dopamine signaling properties in ASD. Therefore, it's crucial to look into other ways to put the dopamine theory of ASD to the test.

DOPAMINE HYPOTHESIS LIMITATIONS IN AUTISM

Autism spectrum disorder is understood to be a condition with numerous underlying causes that affect certain brain circuits. It is therefore conceivable that distinct molecular abnormalities mix in different proportions and result in abnormal signaling in particular brain circuits.[37] Nevertheless, dopamine signaling anomalies have been linked to a number of ASD comorbidities, including executive function impairments, anxiety, tics, and attention-deficit hyperactivity disorder.[28] It is not viable to claim that ASD is

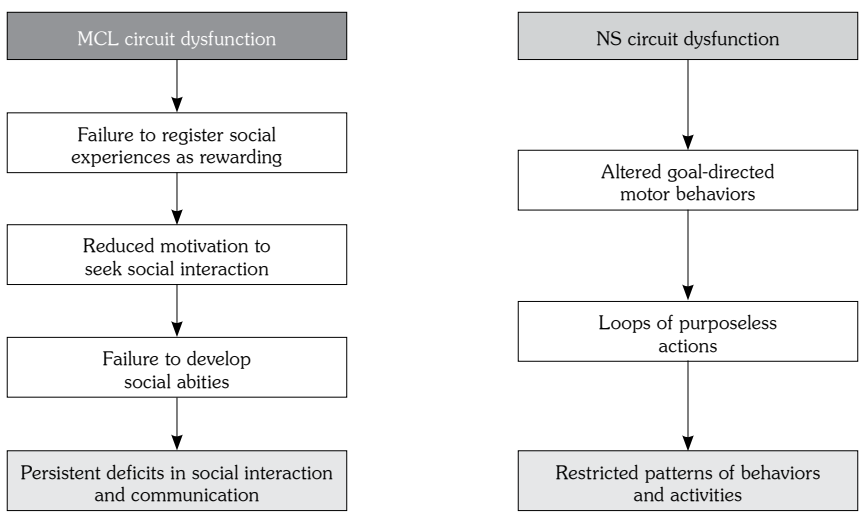

Figure 1. Illustrates the mechanism by which midbrain diffuse dopaminergic modulatory network dysfunction causes autistic core characteristics.

MCL: Mesocorticolimbic; NS: Nigrostriatal.

just a dopamine-signaling issue in light of this information. The neurological basis of ASD is also thought to be influenced by further anomalies in neurotransmitter signaling.[44] In fact, a 2020 article made the case that the pathophysiology of ASD is heavily influenced by aberrant glutamate signaling.[39]

In conclusion, despite the fact that ASD has been linked to a number of different dopamine dysfunctions, it would be incorrect to just blame dopamine deficit for the disorder. It has been hypothesized that autistic-like behavior may affect social motivation and goal-directed motor behavior due to dopamine dysfunctions in extensive dopaminergic modulatory networks in the midbrain. Two fundamental truths about autism have emerged from the research: First, dopamine dysfunctions in particular brain regions can create social deficits and stereotyped behaviors in persons who are not autistic. Second, dopamine modulators can enhance behavior when dopamine dysfunctions are the cause of autism-like behaviors. This idea is supported by the effectiveness of dopamine antagonists in helping autistic individuals with their basic behaviors, which creates a pharmacological connection between dopamine and ASD. Additionally, the discovery of dopaminergic dysfunctions in autistic patients may help researchers better understand disorders with behavioral symptoms, the pathogenesis of neuropsychiatric disorders, and the biological underpinnings of human behavior.

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