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The Role of Glutamate-Related Genes in Neurotransmitter Imbalances in Schizophrenia

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Abstract: Schizophrenia is a severe and chronic mental disorder characterized by profound disruptions in thinking, perception, emotions, and behavior, often leading to impaired reality testing (psychosis), social dysfunction, and cognitive deficits. This paper integrates the neurobiological perspective of schizophrenia with its genetic aspects. While dopamine dysregulation has long been implicated in its pathology, emerging research has emphasized the critical role of glutamatergic neurotransmission. The dopamine hypothesis is one of the primary theories proposed for the development of schizophrenia, as it was found that typical antipsychotics function by blocking dopamine D2 receptors. However, this hypothesis was not able to fully explain the cognitive and negative symptoms of schizophrenia. Thus, a new hypothesis was formed, called the glutamate hypothesis, which postulates that schizophrenia results from the hypofunction of the glutamatergic system, especially by blocking NMDA receptors. Genetic studies have identified several susceptibility genes involved in glutamatergic regulation, including G72 (DAOA), DTNBP1 (dysbindin), GRM3, and NRG1, which modulate synaptic glutamate signaling and receptor function. Understanding these genetic influences provides a more integrative view of the neurobiological mechanisms of schizophrenia, and opens new avenues for targeted treatment strategies beyond the dopaminergic model.

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I. INTRODUCTION

Schizophrenia is a complex psychiatric disorder characterized by disruptions in thoughts, perceptions, and emotions. It is characterized by three core symptom domains: positive symptoms (hallucinations, delusions, disorganized behavior), negative symptoms (avolition, blunted affect, social withdrawal), and cognitive impairments (working memory deficits, executive dysfunction).

Neurobiological dysregulation in schizophrenia is often associated with dopamine (DA) dysregulation. However, emerging research suggests that glutamatergic pathways, particularly those involving the hypofunction of the N-methyl-D-aspartate receptor (NMDAR) and related genes, may play a pivotal role in its onset and maintenance.

Recent advances have shown that the expression of these glutamate-related genes influences neurotransmitter imbalances in schizophrenia, particularly those involving dysregulation of the glutamate pathway and its receptors.[25] This is essential to link the fields of genetics and neurobiology, potentially helping to expand the understanding of schizophrenia, guide new treatment development, and improve diagnosis and patient outcomes. These studies could also eventually reveal new targets for antipsychotic drug treatment, which currently focuses on the inhibition of the dopaminergic system.

II. THE DOPAMINE HYPOTHESIS

Dopaminergic mechanisms have been the primary mechanisms involved in schizophrenia, and dopamine has been the primary neurotransmitter involved in most neurochemical studies of schizophrenia.[16] The dopamine hypothesis, one of the most widely known theories regarding the onset and maintenance of schizophrenia, originated from the fact that the main action of typical antipsychotics is the blockade of dopamine D2 receptors.[22] It postulates that an excess of mesolimbic dopamine is associated with positive symptoms of schizophrenia.[24] However, this hypothesis only accounts for certain aspects of schizophrenia, such as positive symptoms. The core features of schizophrenia, which are primarily responsible for persistent disability, are linked to pervasive cortical pathology and are unlikely to be a consequence of dopamine dysfunction.[2] Dopaminergic dysfunction does not account for the cognitive and negative symptoms of schizophrenia or the pattern of neurocognitive dysfunction in schizophrenia.[17] Additionally, reconceptualization's of this hypothesis suggest that an increased state of dopamine activity may exist in subcortical regions and a decreased state of dopamine activity may exist in cortical regions simultaneously.[30] However, the mechanisms underlying these differences remain unclear. Furthermore, schizophrenia is a heterogeneous disorder that cannot be explained by a single mechanism.

Genetically, according to studies, only one risk locus has been found to be associated with the dopamine system, specifically the dopamine D2 receptor, possibly indicating

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that dopamine might not play as large a role as previously believed.[31] Thus, an alternative hypothesis is required to provide a comprehensive overview of the etiology of schizophrenia.

➢ *Glutamate as a Neurotransmitter*

Glutamate (Glu) is the most abundant excitatory amino acid neurotransmitter, accounting for approximately 60% of neurons and 40% of synapses in the brain.[17] Glutamate receptors are classified into ionotropic and metabotropic subtypes.[26] The three known ionotropic classes, AMPA, kainate, and NMDA receptors, facilitate fast synaptic transmission via ligand-gated ion channels. Additionally, eight G protein-coupled metabotropic receptors (mGluRs) modulate slower neuromodulatory effects.[27] The NMDA receptor consists of two subunit types, NR1 and NR2, with two pairs of each, forming the ion channel structure. [1] The NR2 subunit contains a glutamate binding site, whereas NR1 serves as the binding site for co-agonists glycine and D-serine, also referred to as the glycine modulatory site (GMS). The NMDA receptor plays an essential role in synaptic plasticity, memory formation, and long-term potentiation. However, studying NMDA receptor binding sites presents greater complexity compared to studying AMPA and kainate receptors, due to the presence of multiple well-defined ligand-binding domains. These include distinct sites for glutamate, glycine, polyamines, and an internal channel location where dissociative anesthetics (e.g., phencyclidine) exert their effects.[28]

For proper neural function, glutamate concentration must be precisely regulated at specific locations and timeframes. Neurons require accurate glutamate sensitivity, sufficient metabolic resources to respond to normal stimulation, and efficient removal mechanisms to maintain a balanced extracellular level. Both inadequate and excessive glutamate signaling can have detrimental effects on neuronal viability and circuit function.[3]

➢ *The Glutamate Hypothesis*

Antagonists of the NMDA receptor, such as phencyclidine (PCP), ketamine, and similarly acting psychotomimetic agents were found to induce symptoms similar to those of schizophrenia by blocking neurotransmission at NMDA-type glutamate receptors.

Based on this, glutamate pathways, particularly those involving NMDA receptor-mediated neurotransmission, were seen to have a possible role in schizophrenia. [16 17 18 19] An increasing number of neuropsychiatric disorders, such as schizophrenia, substance abuse, mood disorders, Alzheimer's disease, and autism spectrum disorders, have been linked to disruptions in glutamate-mediated neurotransmission.[29] This hypothesis proposes that hypofunction of the glutamatergic system contributes to the pathophysiology of schizophrenia. A growing body of evidence supports this hypothesis, with multiple studies reporting abnormalities in the expression of NMDAR-associated genes and related metabolic processes in individuals with schizophrenia. [13]

➢ *Glutamate-Related Genes in Schizophrenia*

Recent large-scale genomic studies have identified more than 100 susceptibility loci for schizophrenia through genome-wide association studies (GWAS).[31] These findings strongly implicate dysregulation of glutamatergic signaling pathways in the pathophysiology of the disease. Research has linked numerous genes responsible for the formation and function of glutamatergic synapses to schizophrenia. It is important to note that schizophrenia is a highly polygenic disorder, meaning that its development involves the combined effect of hundreds of genetic variants, each contributing a small risk rather than a single causative gene. This includes genes that facilitate glutamatergic neurotransmission, such as the following genes:

➢ *G72*

G72/D-Amino Acid Oxidase (DAO) is a glutamate-related gene that encodes a protein that activates the D-amino acid oxidase enzyme (DAOA), which metabolizes D-serine. Many studies have demonstrated an association between this gene and schizophrenia. [33 34] Decreased D-serine levels and impaired NMDA receptor activity are likely the fundamental mechanisms underlying the involvement of G72 and DAO in the pathogenesis of schizophrenia. [9] Dysfunction of D-amino acid oxidase due to increased activity of the DAO activator (G72 Gene) leads to decreased D-serine levels.

The G72 gene product regulates D-amino acid oxidase (DAAO), which is the primary enzyme responsible for metabolizing D-serine. D-serine acts as a co-agonist of the glutamate receptor by producing the protein PLG72, which acts as an agonist for the glycine-binding site of the NMDA glutamate receptor, making it essential for the function of the NMDA receptor. [10] This, in turn, is implicated in the pathogenesis of schizophrenia, as altered activity of the G72 gene subsequently leads to NMDA receptor hypofunction. [23] D-serine also modulates neurodevelopmental processes, including neuronal migration and programmed cell death. Thus, G72-mediated alterations in DAAO activity may contribute to the development of schizophrenia.

Specifically, increased DAAO activation can lead to reduced D-serine availability, resulting in NMDA receptor hypofunction. This genetic pathway provides support for the glutamate hypothesis of schizophrenia, suggesting that impaired NMDA receptor signaling may arise partly through dysregulation of the G72-DAAO-D-serine axis.

However, some studies have shown that DAOA decreases DAO activity; thus, its effects remain to be confirmed.[7] According to previous studies, DAOA binds to DAO and enhances its activity[34]. However, other studies [35] demonstrated that DAOA binds to DAO and reduces its activity. As a result, the impact of DAOA on DAO has yet to be elucidated.

➢ *DTNBP1 (Dystrobrevin-Binding Protein 1)*

One of the sites of positive linkage for schizophrenia, chromosome 6p22.3, contains the dysbindin gene (DTNBP1). It is expressed in the prefrontal cortex (PFC),

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making it critical for cognitive processes, such as decision-making and working memory.

Genetic variations in DTNBP1 have been associated with an increased risk of schizophrenia and its cognitive symptoms. This suggests that DTNBP1 plays a role in the development of schizophrenia, through its effect on glutamate signaling.[36] Additionally, studies have investigated the link between DTNBP-1 and glutamate signaling in the context of Schizophrenia.

Dysbindin-1, a protein encoded by DTNBP1, interacts with proteins involved in the release of glutamate, such as vesicular trafficking proteins. Dysbindin is expressed in axon terminals of glutamatergic neurons, and influences glutamatergic function by interacting with vesicular trafficking proteins. [15] This can impact the amount of glutamate released into the synaptic cleft. Dysbindin (DTNBP1) binds to both α- and β-dystrobrevin. It forms part of the dystrophin protein complex found in both muscle and other cell types. The molecular interaction between dysbindin-1 and β-dystrobrevin enables its integration into the dystrophin glycoprotein complex within synaptic regions. This functional association suggests that genetic variations in dysbindin-1 could contribute to schizophrenia susceptibility through modifications in synaptic regulatory mechanisms.[14]

Dysbindin overexpression can increase glutamate release, while dysbindin reduction can decrease glutamate release. [11] Studies have found reduced expression of the DTNBP1 gene in people with schizophrenia, across several brain regions, especially in glutamatergic nerve terminals of the hippocampus. [21] Thus, reductions of DTNBP1 gene expression were observed in the PFC of patients with schizophrenia. These changes in DTNBP1 expression in the PFC contribute to the cognitive symptoms of patients with schizophrenia.[14] However, the exact effect of dysbindin on prefrontal brain function at an underlying neurophysiological level has not yet been explored for schizophrenia patients.[25]

- *GRM3 (Glutamate Metabotropic Receptor 3)*

This is another glutamate-related gene associated with cognitive symptoms. It is a G-protein coupled receptor that influences synaptic glutamate levels. The GRM3 gene plays a role in altering glutamate signaling within the prefrontal cortex and hippocampus, which are key brain regions associated with advanced cognitive processes.[21] Because GRM3 variants are linked to impaired PFC function, their impairment is consistent with cognitive deficits in schizophrenia. Studies have identified a specific single-nucleotide polymorphism (SNP) in GRM3's intron 2 region, which correlates with heightened schizophrenia risk because it has been linked to reduced levels of N-acetylaspartate.[26] Additionally, this genetic variant was also linked to the cognitive deficits commonly observed in the disorder.

- *NRG1 (Neuregulin)*

NRG-1 is closely related to glutamate signaling in the brain by playing a role in regulating the expression and function of glutamate receptors. It increases glutamate uptake by upregulating the expression of excitatory amino acid carrier 1, which is a protein that removes glutamate from the synaptic cleft.[37] It also plays an essential role in neurodevelopment and synaptic plasticity. Research has demonstrated that neuregulin, a multifunctional protein, can suppress NMDA receptor function in the human prefrontal cortex.[38] Importantly, this inhibitory effect on NMDA receptors appears to be significantly stronger in individuals with schizophrenia compared to healthy controls. This suggests that excessive neuregulin signaling may contribute to the NMDA receptor hypofunction characteristic of schizophrenia. [20] [21] Mutations or dysregulation of this signaling pathway have been associated with schizophrenia.

III. DISCUSSION

Genetic variations in G72 (DAOA), DTNBP1, GRM3, and NRG1 contribute to schizophrenia risk by disrupting glutamatergic signaling. G72 interacts with D-amino acid oxidase (DAAO), a co-agonist of NMDA receptors, to regulate D-serine levels. Altered G72 activity reduces NMDA function, which is linked to cognitive deficits.

DTNBP1 encodes the dysbindin-1 protein, which modulates synaptic vesicle trafficking in glutamatergic neurons, and hippocampal deficiency in schizophrenia correlates with impaired glutamate release and synaptic plasticity. GRM3 variants affect metabotropic glutamate receptor 3 (mGluR3), reducing glutamate reuptake and disrupting prefrontal-hippocampal circuitry. Similarly, NRG1 dysregulation affects NMDA receptor function by inhibiting NMDA receptor function in the PFC. This inhibitory effect is stronger in individuals with schizophrenia. Taken together, these genes highlight glutamatergic hypofunction as a central pathway in the pathophysiology of schizophrenia.

IV. LIMITATIONS

While the glutamate hypothesis is able to effectively cover a large variety of symptoms, it does not explain the therapeutic efficacy of dopamine antagonists. These findings imply co-occurring dysfunctions in both neurotransmitter systems in schizophrenia, making it necessary to study their interactions. Additionally, schizophrenia is a complex disorder. Its polygenic nature makes it difficult to understand the effects of a specific gene on its onset. This has led to contradictory findings regarding the impact of certain genes on its onset, such as in the previously mentioned case of the effect of DAOA on DAO. Therefore, further investigations are needed to elucidate the interplay between neurotransmitter systems and genetic factors in schizophrenia.

CLINICAL IMPLICATIONS

The glutamate hypothesis of schizophrenia has crucial clinical implications, particularly for treatment development. Traditional antipsychotics primarily target dopamine receptors and are effective mainly for positive symptoms, yet many patients experience persistent negative and

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cognitive symptoms or are treatment-resistant. Substances that modulate glutamatergic transmission, such as NMDA receptor co-agonists and metabotropic glutamate receptor modulators, show promise in improving a broader range of symptoms. Thus, the glutamate hypothesis and the role of glutamate-related genes can help develop new treatment mechanisms to address all varieties of symptoms. Understanding glutamatergic abnormalities may help explain the pathophysiology of treatment-resistant schizophrenia and guide the use of drugs that may exert some of their effects through glutamatergic pathways.

DIRECTIONS FOR FUTURE RESEARCH

It is important to recognize that both the glutamate and dopamine models, while valuable, provide only partial explanations for the complex pathophysiology of schizophrenia. For example, the glutamate hypothesis does not account for the consistently observed increase in presynaptic striatal dopamine function in patients, nor does it explain why dopamine antagonists are effective for positive symptoms, but not for negative or cognitive symptoms. Additionally, while neurotransmitter models have provided valuable insights, research must now also investigate the fundamental mechanisms underlying gene expression patterns. This research should focus on elucidating the causes of altered gene expression, with particular attention to the role of epigenetic mechanisms. Epigenetics, which bridges genetic and environmental factors, may help identify specific epigenetic modifications, such as DNA methylation patterns and histone modifications, which may serve as biomarkers for early detection, prognosis, and individualized treatment approaches. Exploring the therapeutic potential of agents that can modify epigenetic markers can improve symptom management and treatment response. Therefore, an approach that considers the interplay among multiple neurotransmitter systems, genetic factors, and epigenetic factors is important for advancing our understanding and treatment of schizophrenia.

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