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Review Article

Growth Factors, Cell Receptors, Intracellular Kinases, and Transcription Factors Associated with Schizophrenia

AJ Russo[1]*, Albert Mensah[2] and Judith Bowman[2]

[1]Visiting Professor, Hartwick College Oneonta, NY and Research Director, Mensah Research Institute, Warrenville, Il, USA

[2]Mensah Research Institute, Warrenville, Il, USA

***Corresponding Author:** AJ Russo, Visiting Professor, Hartwick College Oneonta, NY and Research Director, Mensah Research Institute, Warrenville, Il, USA.

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Abstract

Schizophrenia is a complex neuropsychiatric disorder characterized by a range of symptoms, including cognitive deficits, hallucinations, and delusions. The pathophysiology of schizophrenia has been linked to growth factors, cell receptors, intracellular kinases, and transcription factors. This paper is a review of these cellular factors which are associated with the etiology of schizophrenia.

Keywords: *Schizophrenia; Growth Factors; Cell Receptors; Intracellular Kinases*

Growth factors associated with schizophrenia

One of the critical factors implicated in the pathophysiology of schizophrenia is brain-derived neurotrophic factor (BDNF), a neurotrophin that plays a vital role in neuronal survival, growth, and plasticity. Research has increasingly focused on understanding how BDNF levels and genetic variations associated with BDNF influence the development and progression of schizophrenia.

The relationship between BDNF and schizophrenia has been extensively studied, revealing that decreased serum levels of BDNF are often observed in individuals with schizophrenia, particularly in drug-naïve first-episode patients. For instance, reported significantly lower serum BDNF levels in drug-naïve first-episode schizophrenia patients compared to healthy controls, suggesting a potential biomarker role for BDNF in the disorder [1]. This finding is supported by other studies, which demonstrated that BDNF levels can increase during antipsychotic treatment, indicating a possible therapeutic effect of these medications on BDNF signaling [2]. Moreover, highlighted the maldevelopment hypothesis, which posits that abnormal structural development in the brain, potentially influenced by BDNF dysregulation, could contribute to the onset of schizophrenia [3].

Genetic factors also play a significant role in the association between BDNF and schizophrenia. Variants in the BDNF gene, particularly the Val66Met polymorphism, have been linked to altered BDNF expression and may influence the age of onset and symptom severity in schizophrenia patients [4]. Such genetic variations can affect BDNF's ability to promote neuronal survival and synaptic plasticity, which are crucial for normal cognitive functioning. Studies have shown that individuals carrying the Met allele of the BDNF gene may exhibit a higher risk for developing schizophrenia and related cognitive deficits [5]. Furthermore, identified the BDNF gene as a risk factor for schizophrenia in specific populations, reinforcing the genetic component of this neurotrophic factor in the disorder's etiology [5].

The role of BDNF in neurodevelopment is particularly relevant to understanding schizophrenia's pathophysiology. BDNF is essential for the maturation of neurons and the formation of synapses, processes that are often disrupted in schizophrenia. For example, prenatal stress has been shown to lead to dysregulation of BDNF in the brain, which may interfere with normal brain development and increase vulnerability to psychiatric disorders later in life [6]. This aligns with the neurodevelopmental hypothesis of schizophrenia, which posits that early-life stressors and genetic predispositions can lead to abnormal brain development and increased risk for psychosis [7].

Research has also indicated that BDNF levels may correlate with cognitive symptoms in schizophrenia. A systematic review by found that lower BDNF levels were associated with cognitive impairments in schizophrenia patients, suggesting that BDNF could serve as a biomarker for cognitive dysfunction in this population [8]. This is further supported by findings from, who explored the potential of serum BDNF as a biomarker for cognitive enhancement in schizophrenia, indicating that BDNF levels might reflect cognitive recovery following treatment [9].

Moreover, the interaction between BDNF and other neurobiological systems, such as the dopaminergic system, is crucial for understanding schizophrenia. BDNF has been shown to modulate dopamine receptor expression, which is particularly relevant given the dopaminergic dysregulation observed in schizophrenia [10]. This interplay suggests that BDNF not only influences neuronal health but also interacts with neurotransmitter systems that are disrupted in schizophrenia, thereby contributing to the disorder's symptomatology.

In addition to genetic and neurodevelopmental factors, environmental influences, such as stress and substance use, have been implicated in BDNF dysregulation in schizophrenia. For instance, discussed how cannabinoid exposure might affect BDNF levels, highlighting the complex relationship between substance use and neurotrophic factors in the context of schizophrenia [11]. Similarly, studies have shown that physical activity can enhance BDNF levels, suggesting that lifestyle interventions may have therapeutic potential for individuals with schizophrenia [12].

The implications of BDNF research extend to treatment strategies for schizophrenia. Understanding the role of BDNF in the pathophysiology of schizophrenia could lead to the development of novel therapeutic approaches targeting BDNF signaling pathways. For instance, pharmacogenetic studies have suggested that BDNF may serve as a target for optimizing antipsychotic treatments, potentially improving outcomes for patients [13]. Additionally, interventions aimed at increasing BDNF levels, such as aerobic exercise or cognitive training, may offer complementary strategies to traditional pharmacological treatments [12,14].

In conclusion, BDNF is a critical factor in the pathophysiology of schizophrenia, influencing neuronal health, cognitive function, and the overall development of the disorder. The interplay between genetic predispositions, environmental factors, and neurodevelopmental processes underscores the complexity of schizophrenia and highlights the potential for BDNF as a biomarker and therapeutic target. Future research should continue to explore the multifaceted roles of BDNF in schizophrenia, aiming to elucidate its mechanisms and therapeutic implications further.

Cell receptors associated with schizophrenia

The pathophysiology of schizophrenia has been linked to various neurotransmitter systems, particularly the dopaminergic and glutamatergic systems, which involve several receptor types. This synthesis will explore the roles of different cell receptors associated with schizophrenia, focusing on dopamine receptors, glutamate receptors, and GABA receptors, among others.

Dopamine receptors, particularly the D2 subtype, have long been implicated in the pathophysiology of schizophrenia. The dopamine hypothesis posits that hyperactivity of dopaminergic pathways, especially in the mesolimbic system, contributes to positive symptoms of schizophrenia, such as hallucinations and delusions [15]. Antipsychotic medications primarily target D2 receptors to mitigate these

symptoms, highlighting the importance of this receptor in treatment strategies [16]. Furthermore, genetic studies have identified polymorphisms in dopamine receptor genes, suggesting a genetic predisposition to altered dopamine signaling in schizophrenia [17].

In addition to D2 receptors, the role of D3 receptors has garnered attention. Research indicates that D3 receptors are upregulated in the ventral striatum of non-medicated schizophrenia patients, which may contribute to the disorder's symptomatology [17]. The interplay between D3 and glutamate pathways is also significant, as evidence suggests that D3 receptor activation can modulate glutamate release, thereby influencing dopaminergic activity [18]. This relationship underscores the complexity of neurotransmitter interactions in schizophrenia.

Glutamate receptors, particularly the N-methyl-D-aspartate (NMDA) receptor, have been implicated in the pathophysiology of schizophrenia through the glutamate hypothesis. Dysfunction of NMDA receptors is believed to lead to decreased glutamatergic neurotransmission, which can result in dopaminergic dysregulation and contribute to both positive and negative symptoms of schizophrenia [19]. Studies have shown that NMDA receptor antagonists, such as ketamine and phencyclidine, can induce psychotic symptoms like those observed in schizophrenia, further supporting the role of glutamate dysfunction in the disorder [20]. Additionally, the expression of NMDA receptor subunits has been found to be altered in the brains of individuals with schizophrenia, indicating a potential target for therapeutic intervention [16].

Moreover, metabotropic glutamate receptors (mGluRs) have emerged as important players in the schizophrenia pathology. Specifically, mGluR5 hypofunction has been linked to glutamatergic dysregulation in schizophrenia, suggesting that targeting these receptors may offer new treatment avenues [21]. Activation of mGluR1 receptors has been shown to inhibit dopamine release in the meso-striatal system, indicating that mGluRs could modulate dopaminergic activity and potentially alleviate symptoms [22].

GABAergic dysfunction is another critical aspect of schizophrenia, with alterations in GABA receptor expression contributing to the disorder's symptomatology. Studies have demonstrated a selective reduction in GABAA receptor α1 subunit mRNA expression in pyramidal cells of individuals with schizophrenia, which may lead to impaired inhibitory control within neural circuits [23]. This reduction in inhibitory signaling can exacerbate excitatory neurotransmission, further complicating the neurochemical landscape of schizophrenia [24].

Additionally, the role of GABAergic interneurons, particularly parvalbumin-expressing interneurons, has been highlighted in schizophrenia research. These interneurons are crucial for maintaining the balance between excitation and inhibition in the cortex, and their dysfunction has been linked to cognitive deficits observed in schizophrenia [25]. Genetic studies have shown that variations in genes associated with GABAergic signaling, such as those encoding for GAD67, are implicated in the disorder, suggesting a genetic basis for GABAergic dysfunction [26].

The interplay between these receptor systems is complex and multifaceted. For instance, the interaction between dopamine and glutamate systems is critical for understanding the neurobiology of schizophrenia. Dopamine D1 receptors can influence NMDA receptor-mediated transmission, and conversely, NMDA receptor activity can modulate dopaminergic signaling [27]. This reciprocal relationship highlights the need for a comprehensive understanding of how these systems interact in the context of schizophrenia.

Furthermore, the role of neuroinflammation and immune dysregulation in schizophrenia has gained attention in recent years. Abnormalities in cytokine levels and immune markers have been observed in patients, suggesting that immune system dysfunction may contribute to the disorder's pathophysiology [28]. The involvement of receptors such as the complement receptor type 1 in immune signaling pathways further emphasizes the potential link between immune dysregulation and schizophrenia [29].

In summary, the pathophysiology of schizophrenia is intricately linked to various receptor systems, including dopamine, glutamate, and GABA receptors. The dysregulation of these receptors contributes to the complex symptomatology of the disorder and highlights the need for targeted therapeutic strategies that address these neurochemical imbalances. Future research should continue to explore the interactions between these receptor systems and their implications for treatment, as well as the potential role of immune dysregulation in the etiology of schizophrenia.

Intracellular kinases associated with schizophrenia

Recent research has increasingly focused on the role of intracellular signaling pathways, particularly those involving various kinases, in the pathophysiology of schizophrenia. This synthesis will explore the involvement of several key kinases and their associated signaling pathways in the context of schizophrenia, drawing on a wide array of studies that elucidate their roles.

One of the most extensively studied kinases in relation to schizophrenia is Protein Kinase B (AKT). AKT is a serine/threonine kinase that plays a crucial role in various cellular processes, including metabolism, cell proliferation, and survival. Dysregulation of the AKT signaling pathway has been implicated in the pathogenesis of schizophrenia. For instance, studies have shown that decreased levels of phosphorylated AKT (p-AKT) are observed in the frontal cortex of patients with schizophrenia, suggesting a potential link between AKT signaling and the disorder's symptoms [30,31]. Moreover, the AKT pathway interacts with other signaling cascades, such as the glycogen synthase kinase 3 (GSK-3) pathway, which is also implicated in schizophrenia [32].

GSK-3 is another critical kinase that has garnered attention in schizophrenia research. It is involved in numerous cellular processes, including the regulation of neuronal development and synaptic plasticity. Notably, decreased phosphorylation of GSK-3α/β has been reported in post-mortem brain tissue from schizophrenia patients, indicating a potential disruption in its regulatory functions [33]. The interplay between AKT and GSK-3 is particularly relevant, as AKT can phosphorylate and inhibit GSK-3, thereby influencing downstream signaling pathways that are crucial for neuronal health and function [32].

Calcium/calmodulin-dependent protein kinase II (CaMKII) is another kinase of interest in the context of schizophrenia. CaMKII is a key regulator of synaptic plasticity and is involved in the modulation of neurotransmitter signaling. Variants of CaMKII have been identified in patients with schizophrenia, and alterations in its activity may contribute to the cognitive deficits associated with the disorder [34,35]. Furthermore, the dysregulation of CaMKII signaling has been linked to impaired calcium signaling and neurodevelopmental processes, which are critical in the etiology of schizophrenia [34].

The mitogen-activated protein kinase (MAPK) signaling pathway is also implicated in schizophrenia. Abnormalities in MAPK signaling have been observed in postmortem brain studies, particularly in the prefrontal cortex, which is crucial for cognitive functions [36,37]. The MAPK pathway is involved in various cellular responses, including those related to stress and neurotrophic factors, which are essential for neuronal survival and differentiation. Disruptions in this pathway may contribute to the neurodevelopmental aspects of schizophrenia, highlighting its importance in understanding the disorder's etiology [36].

Another significant kinase in the context of schizophrenia is the p21-activated kinase (PAK). PAK is involved in cytoskeletal dynamics and has been shown to interact with signaling pathways that regulate neuronal morphology and synaptic function. Genetic studies have implicated PAK in schizophrenia risk, suggesting that alterations in its signaling may affect synaptic plasticity and contribute to the disorder's symptoms [38,39]. The relationship between PAK and other signaling molecules, such as CDC42, further underscores the complexity of intracellular signaling networks in schizophrenia [39].

Moreover, Src family kinases (SFKs) have been identified as important mediators of NMDA receptor signaling, which is crucial for synaptic transmission and plasticity. Dysregulation of SFK activity has been associated with NMDA receptor hypofunction, a hypothesis that has been proposed to explain some of the cognitive and negative symptoms of schizophrenia [40]. The interplay between SFKs and other kinases, such as AKT and GSK-3, suggests a convergent pathway that may underlie the pathophysiology of schizophrenia [40].

In addition to these kinases, the role of neurotrophins and their associated signaling pathways cannot be overlooked. Brain-derived neurotrophic factor (BDNF) is a key player in neuronal survival and plasticity, and its signaling through TrkB receptors has been linked to schizophrenia. Alterations in BDNF signaling can affect AKT and GSK-3 pathways, further complicating the molecular landscape of schizophrenia [41,42]. The interaction between neurotrophic factors and intracellular kinases highlights the importance of understanding these signaling networks in the context of neurodevelopmental disorders.

Furthermore, the involvement of microRNAs in regulating kinase activity and expression has emerged as a significant area of research. For example, microRNA-137 has been implicated in the regulation of genes associated with glutamate signaling and synaptic plasticity, which are critical in schizophrenia [43,44]. The modulation of kinase signaling by microRNAs may provide additional insights into the molecular mechanisms underlying schizophrenia and its associated symptoms.

In summary, the intricate network of intracellular kinases and their signaling pathways plays a pivotal role in the pathophysiology of schizophrenia. Key kinases such as AKT, GSK-3, CaMKII, PAK, and SFKs are involved in various cellular processes that are disrupted in schizophrenia. Understanding these pathways not only enhances our knowledge of the disorder's etiology but also opens avenues for potential therapeutic interventions targeting these signaling mechanisms. Future research should continue to explore the complex interactions between these kinases and their contributions to the neurodevelopmental and neurobiological aspects of schizophrenia.

Transcription factors associated with schizophrenia

Recent research has increasingly focused on the role of transcription factors (TFs) in the pathogenesis of schizophrenia, revealing that these proteins are crucial in regulating gene expression associated with the disorder. Transcription factors such as TCF4, NF-κB1, and EGR have been implicated in various molecular pathways that contribute to the risk and manifestation of schizophrenia.

Transcription Factor 4 (TCF4) has emerged as a significant player in schizophrenia research. Variants in the TCF4 gene have been associated with increased susceptibility to schizophrenia, particularly through its role in neurodevelopmental pathways. Studies have shown that TCF4 regulates genes involved in neuronal differentiation and synaptic function, which are critical for proper brain development and function [45,46]. The dysregulation of TCF4 has been linked to altered expression of genes that are essential for the development of neural progenitors, further emphasizing its importance in the etiology of schizophrenia [47]. Additionally, TCF4's interaction with other signaling pathways, such as those involved in cellular processes, highlights its multifaceted role in mechanisms that may be disrupted in schizophrenia [48].

Another transcription factor of interest is NF-κB1, which is known to regulate inflammatory responses in the brain. The NF-κB signaling pathway is constitutively active in neural cells and plays a role in the expression of genes associated with neuroinflammation, a process that has been implicated in the pathophysiology of schizophrenia [49]. Elevated levels of NF-κB1 activity have been observed in schizophrenia patients, suggesting that this transcription factor may contribute to the inflammatory processes that characterize the disorder [49]. Furthermore, the interplay between NF-κB1 and long non-coding RNAs (lncRNAs) has been explored, indicating that these regulatory elements may modulate NF-κB1 activity and influence gene expression patterns relevant to schizophrenia [50].

The early growth response (EGR) family of transcription factors, particularly EGR1 and EGR2, has also been implicated in schizophrenia. EGR proteins are known to respond to various stimuli and regulate gene expression involved in neuronal plasticity and survival [51].

Research indicates that EGR transcription factors cooperate with other proteins, such as LIM domain-binding proteins, to drive gene expression changes that may be relevant to the pathogenesis of schizophrenia [51]. The dysregulation of EGR factors could lead to impaired neuronal function and contribute to the cognitive deficits observed in schizophrenia patients.

In addition to TCF4 and NF-κB1, other transcription factors such as GATA2 and MEF2C have been identified as critical regulators in the context of schizophrenia. GATA2 has been shown to be upregulated in schizophrenia samples, and its dysregulation may affect synaptic outgrowth and neuronal connectivity [52]. MEF2C, another transcription factor associated with neuronal development, has been implicated in the regulation of genes that are disrupted in schizophrenia, suggesting that it may play a role in the neurodevelopmental aspects of the disorder [53]. The interplay between these transcription factors and their target genes underscores the complexity of the molecular mechanisms underlying schizophrenia.

Furthermore, the role of microRNAs (miRNAs) in regulating transcription factors has gained attention in schizophrenia research. For instance, miR-132 has been identified as a significant regulator of several transcription factors, including GATA2 and others involved in synaptic function [52]. Dysregulation of miR-132 has been linked to alterations in gene expression patterns associated with schizophrenia, indicating that miRNAs may serve as critical modulators of transcriptional networks in this disorder [52,54]. The interaction between miRNAs and transcription factors highlights a layer of regulatory complexity that may contribute to the pathophysiology of schizophrenia.

The involvement of histone deacetylases (HDACs) in the regulation of transcription factors has also been explored in the context of schizophrenia. Elevated expression of HDAC1 has been reported in the prefrontal cortex of schizophrenia patients, suggesting that epigenetic modifications may influence the activity of transcription factors and, consequently, gene expression [55,56]. This epigenetic dysregulation could lead to altered neuronal function and contribute to the cognitive and emotional symptoms associated with schizophrenia.

Conclusion

In summary, transcription factors play a pivotal role in the molecular mechanisms underlying schizophrenia. Key players such as TCF4, NF-κB1, EGR, GATA2, and MEF2C are involved in regulating gene expression patterns that are critical for neuronal development and function. The dysregulation of these transcription factors, along with the influence of miRNAs and epigenetic modifications, contributes to the complex pathophysiology of schizophrenia. Future research should continue to elucidate the intricate networks of transcriptional regulation in schizophrenia, which may ultimately lead to novel therapeutic strategies targeting these pathways.

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