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Review Article

Growth Factors, Cell Receptors, Intracellular Kinases, and Transcription Factors Associated with Bipolar Disorder

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Abstract

Bipolar disorder (BD) is a complex psychiatric condition characterized by extreme mood swings, including manic and depressive episodes. A growing body of research has highlighted the role of various growth factors, cell receptors, intracellular kinases, and transcription factors associated with the etiology of BP. This review summarizes many of the cellular factors related to BP.

Keywords: *Bipolar Disorder (BD); Growth Factors; Cell Receptors; Intracellular Kinases; Transcription Factors*

Growth factors in bipolar disorder

Bipolar disorder (BD) is a complex psychiatric condition characterized by extreme mood swings, including manic and depressive episodes. A growing body of research has highlighted the role of various growth factors, particularly brain-derived neurotrophic factor (BDNF), in the pathophysiology of bipolar disorder. BDNF is a crucial neurotrophin involved in neurogenesis, neuronal survival, and synaptic plasticity, which are essential for maintaining cognitive functions and emotional regulation. The dysregulation of BDNF has been implicated in mood disorders, including bipolar disorder, suggesting that alterations in BDNF levels may serve as biomarkers for the disease's activity and progression [1,2].

Research has shown that individuals with bipolar disorder often exhibit lower levels of BDNF compared to healthy controls. A systematic review indicated that peripheral BDNF levels are significantly reduced in bipolar disorder patients, particularly during acute episodes [2]. This reduction in BDNF is thought to correlate with the severity of mood symptoms, as evidenced by studies linking lower BDNF levels to increased depressive and manic symptoms [3,4]. Furthermore, the neurotrophic hypothesis posits that mood disorders, including bipolar disorder, are associated with decreased BDNF expression, which may contribute to neuroplasticity deficits and mood dysregulation [4].

The genetic underpinnings of bipolar disorder also intersect with BDNF levels. The Val66Met polymorphism in the BDNF gene has been associated with altered BDNF expression and has been studied for its potential role in the etiology of bipolar disorder. This polymorphism may influence the severity of mood episodes and the overall course of the disorder [5,6]. Studies have shown that

individuals carrying the Met allele may exhibit different neuroanatomical features and BDNF levels, which could further elucidate the relationship between genetic factors and bipolar disorder [7].

In addition to BDNF, other growth factors and inflammatory markers have been explored in the context of bipolar disorder. For instance, vascular endothelial growth factor (VEGF) has been studied for its neurotrophic properties and potential involvement in mood regulation. Low levels of VEGF have been observed in patients with major depressive disorder, suggesting a possible link to bipolar disorder [8] and hepatocyte growth factor as well as ERK ½ have been found to be decreased in Bipolar disease [9,10]. Moreover, inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been found to correlate with mood states in bipolar disorder, indicating that inflammation may play a role in the disorder's pathophysiology [11].

The relationship between BDNF and treatment outcomes in bipolar disorder is another critical area of investigation. Lithium, a common mood stabilizer used in bipolar disorder, has been shown to increase BDNF levels, suggesting that its therapeutic effects may be mediated through neurotrophic mechanisms [12]. Similarly, electroconvulsive therapy (ECT), another treatment modality for severe mood episodes, has been associated with significant increases in BDNF levels, further supporting the notion that enhancing BDNF signaling could be beneficial in managing bipolar disorder [13].

Moreover, the interaction between BDNF and other neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), has been explored in the context of bipolar disorder. Alterations in the expression of these neurotrophic factors may contribute to the neurobiological changes observed in bipolar disorder, including synaptic dysfunction and neuroinflammation [14]. Understanding these interactions could provide insights into the multifaceted nature of bipolar disorder and its treatment.

In summary, the evidence suggests that BDNF plays a pivotal role in the pathophysiology of bipolar disorder, with alterations in its levels being associated with mood episodes and treatment responses. Genetic variations, inflammatory processes, and the impact of therapeutic interventions further complicate the landscape of bipolar disorder research. Continued exploration of BDNF and other growth factors may yield valuable insights into the mechanisms underlying bipolar disorder and inform the development of targeted therapies.

Cell receptors in bipolar disorder

Bipolar disorder (BD) involves multifaceted systems, including glutamatergic, GABAergic, and cholinergic systems, which are mediated by specific cell receptors. Understanding the role of these receptors is crucial for elucidating the pathophysiology of bipolar disorder and developing effective treatments.

One of the most significant receptor systems implicated in bipolar disorder is the glutamate receptor system, particularly the N-methyl-D-aspartate (NMDA) receptors. Abnormalities in NMDA receptor expression and function have been observed in individuals with bipolar disorder, suggesting a potential disruption in glutamatergic signaling that may contribute to mood dysregulation [15,16]. The NMDA receptor is essential for synaptic plasticity and memory function, and its dysregulation could lead to the cognitive impairments often seen in bipolar disorder [16]. Furthermore, studies have indicated that increased glutamate levels in the brain are associated with excitotoxicity, which can result in neuronal damage [17,18].

In addition to NMDA receptors, metabotropic glutamate receptors (mGluRs) also play a critical role in bipolar disorder. For instance, mGluR6, which is predominantly expressed in retinal bipolar cells, has been shown to mediate synaptic responses to glutamate [19]. The functional remodeling of these receptors in response to sensory experience suggests that alterations in mGluR signaling may influence the development and progression of bipolar disorder [20]. Moreover, the interaction between mGluRs and other neurotransmitter systems, such as dopaminergic and GABAergic systems, highlights the complexity of receptor signaling in mood regulation [21].

GABAergic receptors, particularly GABA_A receptors, have also been implicated in bipolar disorder. Alterations in the expression of GABA_A receptor subunits have been observed in individuals with bipolar disorder, indicating a potential dysregulation of inhibitory neurotransmission [22]. The balance between excitatory (glutamatergic) and inhibitory (GABAergic) signaling is crucial for maintaining mood stability, and disruptions in this balance may contribute to the manic and depressive episodes characteristic of bipolar disorder [23]. Furthermore, genetic studies have identified associations between GABA_A receptor subunit genes and bipolar disorder, suggesting a hereditary component to these receptor abnormalities [24].

Muscarinic receptors, particularly the M2 subtype, have also been studied in the context of bipolar disorder. Research has shown decreased binding of muscarinic receptors in the frontal cortex of individuals with bipolar disorder, which may be linked to cognitive deficits and mood dysregulation [25,26]. The cholinergic system's involvement in mood regulation further emphasizes the need to explore the role of muscarinic receptors in bipolar disorder and their potential as therapeutic targets.

Dopaminergic receptors, particularly D2 receptors, have been implicated in the pathophysiology of bipolar disorder as well. Studies have shown that alterations in dopamine receptor sensitivity may contribute to the manic and depressive phases of the disorder [27]. The interplay between dopamine and other neurotransmitter systems, such as glutamate and GABA, underscores the complexity of mood regulation and the potential for receptor-targeted therapies in managing bipolar disorder.

In summary, the involvement of various cell receptors, including NMDA, mGluR, GABA_A, muscarinic, and dopaminergic receptors, is critical in understanding the neurobiological basis of bipolar disorder. Dysregulation of these receptors can lead to imbalances in neurotransmitter signaling, contributing to the mood instability characteristic of the disorder. Future research should focus on elucidating the specific mechanisms by which these receptors influence mood regulation and exploring their potential as targets for novel therapeutic interventions.

Intracellular kinases in bipolar disorder

Recent research has increasingly focused on the role of intracellular kinases in the pathophysiology of bipolar disorder, particularly in relation to signaling pathways that influence mood regulation and neuronal plasticity. This response synthesizes the current understanding of various intracellular kinases associated with bipolar disorder, highlighting their potential roles in the disorder's etiology and treatment.

One of the most extensively studied kinases in the context of bipolar disorder is glycogen synthase kinase-3 (GSK-3). GSK-3 is a serine/threonine kinase that plays a crucial role in various cellular processes, including metabolism, cell differentiation, and apoptosis. Dysregulation of GSK-3 has been implicated in mood disorders, particularly bipolar disorder. Studies have shown that lithium, a common treatment for bipolar disorder, inhibits GSK-3 activity, which may contribute to its mood-stabilizing effects [28,29]. Furthermore, GSK-3 has been associated with the regulation of brain-derived neurotrophic factor (BDNF), a key player in neuroplasticity and mood regulation [30]. Elevated GSK-3 activity has been observed in patients experiencing manic episodes, suggesting that GSK-3 may be a critical target for therapeutic intervention [31].

In addition to GSK-3, protein kinase C (PKC) has garnered attention for its role in bipolar disorder. PKC is a family of serine/threonine kinases that are activated by diacylglycerol (DAG) and play a significant role in signal transduction pathways. Abnormal PKC activity has been reported in bipolar disorder, particularly during manic episodes [31,32]. Research indicates that elevated PKC activity may contribute to the pathophysiology of bipolar disorder by influencing neurotransmitter release and neuronal excitability

[31]. Furthermore, the inhibition of PKC has been shown to rescue manic-like behaviors in animal models, reinforcing the notion that PKC signaling is a potential target for therapeutic strategies [31].

Another important kinase in the context of bipolar disorder is the mitogen-activated protein kinase (MAPK) pathway, which includes extracellular signal-regulated kinases (ERK). The MAPK pathway is involved in various cellular functions, including proliferation, differentiation, and survival. Dysregulation of the MAPK pathway has been implicated in mood disorders, with evidence suggesting that alterations in ERK signaling may contribute to the development of bipolar disorder [33,34]. For instance, increased ERK activity has been observed in the brains of individuals with bipolar disorder, indicating a potential link between ERK signaling and mood dysregulation [33].

Calcium signaling is another critical aspect of intracellular signaling in bipolar disorder. Dysregulation of intracellular calcium levels has been implicated in the pathophysiology of bipolar disorder, with studies demonstrating altered calcium responses in neurons from patients with the disorder [35,36]. Calcium-dependent kinases, such as calcium/calmodulin-dependent protein kinase (CaMK), may play a role in mediating the effects of calcium dysregulation on neuronal function and mood stability [35]. The interplay between calcium signaling and other intracellular kinases, such as GSK-3 and PKC, underscores the complexity of the signaling networks involved in bipolar disorder [33,35].

Diacylglycerol kinases (DGKs) are another group of enzymes that have been linked to bipolar disorder. DGKs regulate the levels of DAG, a key second messenger involved in PKC activation. Genetic studies have identified associations between DGK genes and bipolar disorder, suggesting that alterations in DGK activity may influence mood regulation [36,37]. The role of DGKs in modulating intracellular signaling pathways highlights their potential as therapeutic targets for bipolar disorder.

In summary, intracellular kinases play a pivotal role in the pathophysiology of bipolar disorder, influencing various signaling pathways that regulate mood and neuronal function. Akt, GSK-3, PKC, MAPK, calcium-dependent kinases, and DGKs are among the key kinases implicated in the disorder. Understanding the intricate interplay between these kinases and their signaling pathways may provide valuable insights into the mechanisms underlying bipolar disorder and inform the development of targeted therapeutic interventions (See a summary of the Akt pathway and how it is signalled aby growth hormones and eventually signals transcription factors in the nucleus - Figure 1).

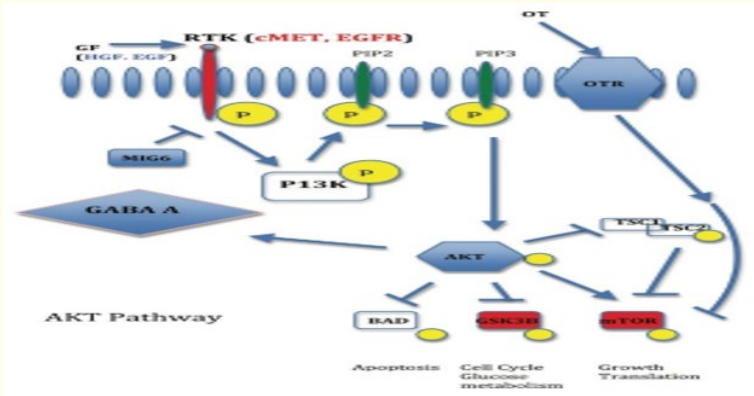

Figure 1: *The Akt pathway may begin with a growth factor (EGF or HGF) binding to the membrane RTK (cMET or EGFR). A cascade of activation ensues when the cytoplasmic portion of the RTK is phosphorylated, which, in turn, reacts with P13K. At the end of the cascade, pathway proteins such as mTOR and GSK3 are affected.*

Transcription factors in bipolar disorder

Recent research has elucidated the role of various transcription factors in the pathophysiology of bipolar disorder, suggesting that these proteins are crucial in regulating gene expression related to mood regulation, neuroinflammation, and neuronal plasticity. This response synthesizes the current understanding of key transcription factors associated with bipolar disorder, drawing on relevant studies to elucidate their roles in the disorder's etiology and potential treatment.

One of the most prominent transcription factors implicated in bipolar disorder is nuclear factor kappa B (NF-κB). NF-κB is a critical regulator of immune responses and inflammation, and its activation has been linked to various neuropsychiatric disorders, including bipolar disorder. Studies have shown that the NF-κB complex is activated in the prefrontal cortex of individuals with bipolar disorder, suggesting a role in the immune activation observed in the disorder [38]. The activation of NF-κB can lead to the transcription of pro-inflammatory cytokines, which may contribute to the neuroinflammatory processes associated with mood dysregulation [38,39]. Furthermore, chronic administration of mood stabilizers, such as lithium and valproate, has been shown to decrease markers of inflammation regulated by NF-κB, indicating that targeting this transcription factor may be beneficial in managing bipolar disorder [39].

Another transcription factor of interest is Sp4, a member of the Sp family of transcription factors. Research has indicated that Sp4 is reduced in the cerebellum of individuals with bipolar disorder, and its expression is regulated by depolarization and lithium treatment [38]. Sp4 is involved in various neuronal processes, including synaptic plasticity and memory formation. Altered expression of Sp4 may contribute to cognitive deficits observed in bipolar disorder, as reduced Sp4 levels have been associated with memory impairments in animal models [40,41]. Additionally, Sp4 has been shown to interact with other transcription factors, such as Sp1, suggesting a complex regulatory network that may influence gene expression in bipolar disorder [40,41].

The transcription factor TCF4 (transcription factor 4) has also been implicated in bipolar disorder. TCF4 is a basic helix-loop-helix transcription factor associated with several neuropsychiatric disorders, including schizophrenia and bipolar disorder. Genetic studies have identified rare mutations in TCF4 that disrupt synaptic function, potentially contributing to the pathophysiology of bipolar disorder [42]. TCF4's role in regulating genes involved in neurotransmission and neuronal development underscores its importance in mood regulation and the potential impact of its dysregulation in bipolar disorder [42,43].

Additionally, the SEF2-1 gene, which encodes a transcription factor, has been linked to bipolar disorder through genetic studies. The presence of expanded CTG18.1 alleles within the SEF2-1 gene has been associated with altered expression of this transcription factor, which may have profound effects on cellular processes in the brain [44]. The dysregulation of SEF2-1 could influence neuronal function and contribute to the mood instability characteristic of bipolar disorder.

Moreover, the transcription factor AP-2 (activating protein 2) has been implicated in the regulation of genes associated with neuroinflammation and excitotoxicity in bipolar disorder. Research has shown that chronic administration of mood stabilizers can decrease markers of excitotoxicity and inflammation, including those regulated by AP-2 [39]. This suggests that AP-2 may play a role in the neurobiological changes observed in bipolar disorder and that targeting this transcription factor could have therapeutic implications.

Conclusion

In summary, transcription factors such as NF-κB, Sp4, TCF4, SEF2-1, and AP-2 play crucial roles in the pathophysiology of bipolar disorder. These factors are involved in regulating gene expression related to inflammation, neuroplasticity, and neuronal function, all of which are critical for mood regulation. Understanding the intricate interplay between these transcription factors and their signaling pathways may provide valuable insights into the mechanisms underlying bipolar disorder and related neurobehavioral disorders, and inform the development of targeted therapeutic interventions [45-47].

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