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GSK3: The Shared Target of Circadian Rhythm and Lithium Treatment in Bipolar Disorder

Puyuan Ge

Department of Medical Imaging, Inner Mongolia Medical University, Inner Mongolia, China
Corresponding author: 1807050107@stu.hrbust.edu.cn

Abstract:

Bipolar disorder is a severe emotional disorder that causes significant damage to patients' cognitive functions. Although the clinical manifestations of bipolar disorder are clear, its pathophysiological mechanisms are currently not well understood. The theme of this review is to explore the pathophysiological mechanisms of bipolar disorder. Starting from the lithium treatment mechanism, the author identified an important target - GSK-3, by reviewing previous literature. Research has shown that GSK-3 plays a crucial role in the bipolar disorder. This review provides an introduction to GSK-3 and its probable mechanisms that contribute to bipolar disease. It also examines the role of GSK-3 in bipolar disorder from both the standpoint of how it develops and how it might be treated. By studying GSK-3, we can augment our comprehension of bipolar disorder and further delve into our grasp of this condition.

Keywords: Bipolar Disorder, Circadian Rhythm, Lithium, GSK-3

1. Introduction

The human circadian rhythm system, formed by a group of approximately 24-hour internal clocks in the body, regulates various biological activities such as body temperature, endocrine function, and sleep/weak cycles [1]. The suprachiasmatic nucleus (SCN) of the hypothalamus has a network of interconnected oscillating neurons that serve as the central pacemaker for the circadian rhythm. This master clock synchronizes peripheral clocks throughout the body with external light cues [2]. The core genes of the biological clock include CLOCK, BMAL, PER, CRY, etc., which form a transcription-translation feedback loop. Emerging studies indicate that the disturbance of circadian rhythm is a significant factor in the onset of multiple diseases, such as cancer, obesity, diabetes, Alzheimer's, Parkinson's, bipolar disorder (BD), and depression [3-5].

Patients with bipolar disorder experience extreme pathological emotional periods characterized by the alternation of manic and depressive symptoms. For most patients, the duration of depressive episodes is longer than that of manic episodes, and depression is the leading cause of bipolar disorder. The depressive symptoms of bipolar disorder are similar to those of common depression. Manic symptoms are not limited to elevated mood but also include reduced sleep, reckless behavior, and, in severe cases, delusions and hallucinations [6]. According to previous meta-analyses, patients with bipolar disorder experience varying degrees of impairment in attention, speech learning, memory, and executive function [7]. The dangers of bipolar disorder are well known, but the causes of bipolar disorder are not well understood. Although there is evidence of changes in brain structure and alterations in a series of biomarkers such as mitochondrial function, inflammation, dopamine, and circadian rhythms in patients with bipolar disorder [8], these discoveries have not been integrated to elucidate its pathophysiology.

Lithium has traditionally been the primary treatment for bipolar disorder. It efficiently manages both the immediate and ongoing symptoms of depression or mania. Although there are now other drugs that have been proven to treat bipolar disorder, such as corticosteroid receptor antagonists like mifepristone and dopamine agonists like pramipexole, lithium remains the only medication with an anti-suicidal effect [9]. Although the therapeutic properties of lithium are well acknowledged, the precise mechanism by which it works is still not fully understood.

Starting from the target of lithium therapy, the author identified GSK-3 as a crucial target in bipolar illness by examining prior trials. This review mainly discusses the following issues: 1) The function of GSK-3 and the mechanism by which it leads to bipolar disorder; 2) How circadian rhythm disruption affects the activity of GSK-3; 3) The mechanism by which lithium impacts GSK-3. Given the fragmented and diverse etiology and treatment modalities of bipolar disorder, there is a need for a more com-

prehensive and clear understanding of bipolar disorder for clinical physicians. The remaining part of this review will introduce a pivotal common target from different perspectives. Ultimately, it is hoped that this review can provide helpful information for clinical physicians to help enhance their understanding of bipolar affective disorder.

2. Common Target of Circadian Rhythm and Lithium in Bipolar Disorder

2.1 Common Target--GSK-3

2.1.1 GSK-3 and its normal function

In vivo, Glycogen synthase kinase-3 (GSK-3) phosphorylates serine and threonine residues of proteins. In the 1990s, the discovery of GSK-3 initially occurred in specific muscles of rabbits [10], and it was associated only with the phosphorylation and inhibition of glycogen synthase. Subsequently, researchers identified two different and highly conserved genes comprising the GSK-3 gene family: GSK-3alpha and GSK-3beta. These genes encode distinct proteins, and these proteins play their respective roles in other pathways. As the study of GSK-3 continues, many researchers have pointed out that countless signaling pathways, such as apoptosis, cell survival, stress response, glycogen synthesis, gene transcription, and cell proliferation, require GSK-3 [11]. Recent research has revealed that GSK-3 displays abnormal behavior in various disorders, including endocrine, neurological, and circulatory diseases. Given its involvement in several pathways, such as the classical Wnt signaling pathway and PI3K/PIP3/PKB signaling pathway, it may be inferred that GSK-3 could be an important target for therapeutic interventions in various disorders.

2.1.2 Possible mechanisms of GSK-3 Causing Bipolar Disorder

Serotonin (5-HT) is a broadly functioning neurotransmitter that greatly influences mood, sleep, appetite, memory, and learning. 5-HT receptor subtypes and related signaling pathways are key points through which 5-HT exerts various functions. 5-HT receptor family at least contains seven different families and 14 different subtypes of 5-HT receptors [12], each of which plays a distinct role in a different tissue or organ.

The 5-HT1B receptor serves two roles in the brain: it acts as an autoreceptor and a heteroreceptor. When 5-HT1BR agonists activate the heteroreceptors, the heteroreceptors can achieve antidepressant effects by affecting the dopamine signaling pathway. Previous studies have shown that humans and rats 5-HT1BR contain eight GSK-3 consensus phosphorylation sites. Ser154 is one of the sites, and Thr158 may be the initiation site for docking GSK-3 on the i2 loop of 5-HT1BR. Subsequently, GSK-3 adds phosphate groups to 5-HT1BR, enhancing its ability to transmit signals and activate Akt and Gi, a heterotrimeric G protein. The influence of GSK-3 is unique because phosphorylated 5-HT1BR cannot respond to agonists without GSK-3's function [13]. Given that the activation of 5-HT-1BR depends on GSK-3, the extent of GSK-3 enzymatic function under normal conditions may have a crucial impact on the activation and functioning of the receptor. The malfunction of GSK-3 can impact the functioning of 5-HT1BR, subsequently affecting neurotransmitter release in the brain and potentially leading to mood disorder.

2.2 Circadian Rhythm Disruption causing Bipolar Disorder by influencing GSK-3

The connection between Circadian rhythm and Bipolar disorder is particularly evident, where patients often suffer from significant sleep disturbances and have different levels of melatonin compared to healthy individuals [14]. The mechanism by which circadian rhythm disruption leads to bipolar disorder is still unclear. However, the discovery of GSK-3 suggests that it may be one of the targets involved in circadian rhythm disruption. This review will discuss the two possible mechanisms by which circadian rhythm may affect GSK-3 and lead to bipolar disorder.

2.2.1 Circadian Rhythm Disruption-affecting GSK-3 by influencing Insulin signaling pathway

In the human brain, insulin primarily participates in two signaling pathways: the PI3K/PIP3/PKB pathway and the Raf/Ras/MAPK pathway. Experiments by Grillo et al. have shown that mice with downregulated hypothalamic insulin receptors exhibit significant depressive and anxious behaviors [15]. However, it is still unclear which pathway insulin utilizes to achieve these effects. Other studies and animal experiments have indicated that mice with dysfunctional CLOCK/BMAL genes display apparent insulin resistance [16], suggesting that circadian rhythm disruption can impact the normal function of insulin receptors. Cross and Alessi confirmed in 1995 that PI3K and Akt activation suppresses GSK-3 [17]. Therefore, circadian rhythm disruption may alter the activity of GSK-3 by affecting the insulin signaling pathway, thereby inducing bipolar disorder

2.2.2 Circadian Rhythm influencing GSK-3 by Wnt signaling pathway

The Wnt signaling pathway is crucial in mammals, guiding many activities such as maintaining stem cells and neurodevelopment. Current research also suggests that Wnt is involved in the pathogenesis of bipolar disorder.

The traditional Wnt pathway comprises a cell surface re-

ceptor/co-receptor complex, an Axin acting as a pedestal, two protein kinases CK1α and GSK-3, a cofactor APC, and a signaling protein β-catenin. Axin provides sites for binding other components. CK1α and GSK-3 enzymes phosphorylate β-catenin at distinct locations. CK1α phosphorylates β-catenin at serine-45, while GSK-3 phosphorylates it at ser33, ser37, and thr41. And APC can directly attach to β-catenin and increase the GSK-3's phosphorylate function. Before accessing the nucleus, β-catenin that has undergone phosphorylation is subjected to ubiquitination, followed by degradation by a proteasome. When the secreted Wnt molecule attaches to the Frizzled receptor (FZD) on the surface of a cell, it recruits the low-density lipoprotein receptor-related protein (LRP) 5 or 6 (LRP5/6) to activate the Wnt pathway. As a consequence, LRP5/6 undergoes phosphorylation, leading to the recruitment of Axin, inhibition of GSK-3, and initiation of a series of subsequent reactions. These processes result in the separation of β-catenin from the Axin and, later, the β-catenin buildup. β-catenin that has built up over time enters the nucleus of the cell and initiates the process of transcribing Wnt target genes. [18],[19].

Clock genes are involved in stimulating and suppressing the classical Wnt pathway. Li conducted a study which discovered that excessive BMAL suppresses GSK-3, resulting in the activation of the Wnt/β-catenin pathway [20]. Therefore, the disturbance of circadian rhythm may have a role in bipolar disorder.

2.2.3 counteracting effects of GSK-3 on Circadian Rhythms

As mentioned above, circadian rhythm can regulate the activity of GSK-3. Conversely, GSK-3β has the ability to add a phosphate group to and enhance the stability of the orphan nuclear receptor Rev-ERBα, which can form a negative feedback pathway to stabilize circadian rhythms by inhibiting the transcription of BMAL. Additionally, GSK-3 targets PER, phosphorylating its PER and promoting the PER/CRY nuclear translocation process, which forms a deterrent protein complex with CLOCK/BMAL to regulate circadian rhythms. Abnormal GSK-3 activity may lead to disruption of circadian rhythms and subsequently induce bipolar disorder [21],[22].

2.3 Lithium's treatment and GSK-3

2.3.1 Lithium in BD's Treatment

Nowadays, some studies suggest that lithium exerts its therapeutic effects through mechanisms related to neuronal plasticity. Nevertheless, the prevailing belief is that lithium is used primarily as a GSK-3 inhibitor for the treatment of bipolar illness. In this review, the author focuses only on the relationship between lithium and GSK-3.

2.3.2 Overall effects of Lithium treatment

Although there is still incomplete research on lithium, its therapeutic effects are unquestionable. According to an evaluation conducted by Moreira and Geoffory, lithium has been found to delay the stages of sleep-wake rhythms and reduce the amplitude of activity rhythms in patients. Additionally, it reduces the length of activity patterns and postpones the highest point of the body's circadian temperature cycle. Long-term administration of lithium helps stabilize the regular patterns of free activity by enhancing the regularity of daily activities, which seems dependent on the dosage [23]. Furthermore, a study conducted on mice demonstrated that long-term administration of lithium resulted in elevated levels of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) in both neurons and glial cells [24]. Additional research has indicated that Lithium enhances neurogenesis via modulating the activity of B-cell lymphoma 2 and tumor protein p53, leading to an increase in the number of neurons, glial cells, and astrocytes in the hippocampus and other regions. These findings suggest that lithium has a neuroprotective impact [25]. Aside from the described effects in the appeal, lithium exhibits additional effects, including antioxidant properties and stimulation of the HPA axis in living organisms, which will not be reiterated in this context.

2.3.3 Mechanisms by which Lithium Affects GSK-3

GSK-3 belongs to the CMGC protein kinase family, and the functioning of CMGC in the body depends on the involvement of magnesium ions. Lithium competitively inhibits magnesium ions of the same ionic radius in different situations, thereby inhibiting GSK-3. Some studies have shown that other monovalent cations do not have the same effect as lithium, and this effect of lithium is not related to the type of anion [26].

Lithium has the potential to indirectly affect the activity of GSK-3 via activating Akt. Typically, when the D2 dopamine receptor (D2R) is activated, it sets off a series of events involving Akt, protein phosphatase 2A (PP2A), and β-arrestin 2 (βArr2). These components come together to create a signal transduction complex that deactivates Akt, therefore removing the inhibition of GSK-3. In experiments conducted in vivo and in vitro, Therapeutic dosages of lithium have been demonstrated to induce the dissociation of the Akt-βArr2-PP2A signal transduction complex. Current research suggests that the interaction between Akt and βArr2 requires the participation of magnesium. The competitive interaction between lithium and magnesium is one of the reasons for the instability of this signal trans-

duction complex [27].

3. GSK-3 becoming an essential factor of Circadian Rhythm and Lithium in BD

GSK-3 plays a role in the development and treatment of bipolar illness through many pathways. Firstly, circadian rhythm disruption alters the function of the Wnt pathway and insulin signaling pathway, causing changes in GSK-3's activity. Then, the abnormal GSK-3 activity affects the normal functioning of the 5-HT system and interacts with the circadian rhythm system, potentially triggering bipolar disorder. Ultimately, lithium, a widely recognized inhibitor of GSK-3, can improve the clinical symptoms of bipolar disorder by directly or indirectly inhibiting GSK-3. However, the effects of lithium's treatment cannot be fully replicated by the GSK-3 inhibitor. This indicates that aside from the pathways mentioned earlier, GSK-3 is involved in many other pathways in the body, and several pathways unrelated to GSK-3 are also involved in the development of bipolar illness. Although not fully explanatory, GSK-3 has a vital function in bipolar illness.

4. Summary

Recent literature reveals that glycogen synthase kinase-3 (GSK-3) plays a multifaceted role in bipolar disorder, linking circadian rhythm disruptions to the disorder's pathogenesis. Circadian rhythm disruption can lead to insulin resistance and overexpression of the BMAL gene, which in turn modifies GSK-3 activity through both insulin signaling and Wnt pathways. Subsequently, abnormal activity of GSK-3 can affect the 5-HT1B receptor in the 5-HT system and the orphan nuclear receptor Rev-erbα in the transcription process of clock genes, thereby triggering bipolar disorder. From a therapeutic perspective, lithium can hinder the activity of GSK-3 by competing with the magnesium ion for its binding site and influencing the Akt-βArr2-PP2A signaling transduction complex. This provides us with a thorough awareness of the pathogenesis of bipolar disorder, assisting us in comprehending the pathophysiology of bipolar illness. Future research should focus on additional GSK-3 pathways to enrich our comprehension of its role in bipolar disorder and to further elucidate the condition's pathophysiology.

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