

Neuromolecular Etiology of Bipolar Disorder: Possible Therapeutic Targets of Mood Stabilizers

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Bipolar disorder is a mental illness that causes extreme mood swings and has a chronic course. However, the mechanism by which mood episodes with completely opposite characteristics appear repeatedly, or a mixture of symptoms appears, in patients with bipolar disorder remains unknown. Therefore, mood stabilizers are indicated only for single mood episodes, such as manic episodes and depressive episodes, and no true mood-stabilizing drugs effective for treating both manic and depressive episodes currently exist. Therefore, in this review, therapeutic targets that facilitate the development of mood stabilizers were examined by reviewing the current understanding of the neuromolecular etiology of bipolar disorder.

KEY WORDS: Bipolar disorder; Drug therapy; Neurobiology.

INTRODUCTION

The ancient Greeks were aware of bipolar disorder; however, medical research of bipolar disorder did not start until the 20th century after it became recognized as a disease. Efforts were made to investigate the etiology of bipolar disorder, with a focus on neurotransmitters. Recently, brain imaging research techniques have rapidly advanced neuromolecular biology research, enabling the discovery of novel findings involving altered brain structures or neurotransmission. In the present review, the etiology of bipolar disorder was evaluated by reviewing the literature to identify upcoming research trends. In particular, the neuromolecular therapeutic targets of mood stabilizers in terms of the pathophysiology of bipolar disorder were summarized and the potential of personalized medicine reviewed.

NEUROTRANSMITTERS

In bipolar disorder, neurotransmitters are abnormally regulated in the brain. Biogenic amine neurotransmission functions in the limbic system are impaired, influencing sleep, appetite, alertness, sexual function, endocrine function, and the regulation of emotions such as fear and anger [1]. Neurotransmitters have been the focus of numerous studies of the pathogenesis of bipolar disorder.

Noradrenaline

The noradrenaline level is usually low in subjects with bipolar disorder; however, the increase in noradrenaline secretion is greater than that in unipolar depression [2]. In addition, the level of 3-methoxy-4-hydroxyphenylglycol, the noradrenaline metabolite, increases during a manic episode [2]. These findings indicate that noradrenaline secretion and conversion increase in depression, and noradrenaline activities increase in manic episodes. The noradrenaline increase may be due to the low sensitivity of inhibitory α_2 -adrenaline receptors, although there is controversy as to whether the low sensitivity is specific to bipolar disorder pathophysiology because the low sensitivity of α_2 -

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adrenaline also occurs in panic disorder. Noradrenaline levels may indicate the degree of anxiety in general rather than characterizing specific syndromes such as depression or mania. However, the response to lithium is associated with the level of 3-methoxy-4-hydroxyphenylglycol; thus, noradrenaline changes likely reflect the clinical features of bipolar disorder to some degree [3,4].

Lithium is used to treat manic episodes and affects the noradrenaline system differently in various brain regions, showing two bimodal effects over time [5]. Lithium initially decreases β -adrenaline receptor functions due to noradrenaline, triggering inhibition of 3',5'-cyclic adenosine monophosphate (cAMP) accumulation, and then acts on the presynaptic α_2 -autoreceptor. The presynaptic α_2 -autoreceptor inhibits noradrenaline secretion, thereby increasing noradrenaline secretion [6,7]. Carbamazepine can decrease noradrenaline conversion and upregulate the β -adrenaline receptor over an extended period; however, the adenylate cyclase (AC) activity triggered by the β -adrenaline receptor is decreased by direct suppression of AC catalyst subunits [8].

Serotonin

Much evidence supports a link between serotonin and mood disorders [9,10]. A relatively high cerebrospinal fluid (CSF) concentration of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, was associated with suicide occurrence and the appearance of aggressive behaviors [11]. This result was based on findings from patients with unipolar depression. Although studies on bipolar disorder exist, the study samples were small, and the influence of serotonin was not clearly explained.

Findings from previous studies vary regarding changes in the CSF level of 5-HIAA in patients with manic depressive episodes [12]. In some studies, a significant difference in the CSF level of 5-HIAA between patients with manic depressive episodes and those with depression was not found. In other studies, a higher correlation of CSF 5-HIAA with the frequency of suicide and aggressive behavior compared with depressive symptoms was reported. However, the decrease in the CSF 5-HIAA level was not evident in patients with bipolar disorder or patients who attempted suicide [13,14].

Dopamine

Mood changes (feelings of highs and lows), as well as

changes in motivation and exercise patterns, are significant clinical signs observed in bipolar disorder. The dopamine system plays an essential role in activity level, motivation control, and compensation circuit in the mid-brain [15]. In an animal model study of depression, decreased dopamine secretion in mesocorticolimbic neurons was reported [16]. The CSF level of homovanillic acid (HVA), a dopamine metabolite, is also decreased in depression but increased during a manic episode [17]. In patients in a depressive state, the CSF level of HVA is decreased. The change in psychomotor speed observed in depression is likely associated with dopamine abnormalities. In a previous study, the decrease in HVA level was greater in patients with psychomotor retardation than in patients with irritable depression [18]. Furthermore, in an observational study, whether the presence or absence of accompanying psychotic symptoms was associated with dopamine, as evidenced by the relatively greater increase in the HVA level in psychotic depression, was investigated [18]. Dopamine, more than other neurotransmitters, has been implicated in the transition of depression to a manic episode in bipolar disorder [19]. This theory is supported by the following evidence: manic episodes typically occur at the time of administration of the dopamine precursor L-dopa; amphetamine, a promoter of dopamine secretion and inhibitor of dopamine absorption, causes hypomanic episodes in patients with bipolar disorder and hypomanic-like episodes in healthy controls; antipsychotics, which block the dopamine receptor, are efficacious for treating manic episodes [20,21]. In addition, after administering amphetamine to patients with bipolar disorder, more significant behavioral changes were observed in the experimental group than in the control group, although no significant difference in dopamine secretion was found [22]. This indicates that dopamine reactivity should increase postsynaptically in patients with bipolar disorder [23]. Antipsychotic drugs can also provide an effective treatment for manic episodes. Drugs stimulating dopamine receptors (e.g., dopamine agonists and dopamine reuptake inhibitors) have antidepressant effects. Lithium, a mood stabilizer, increases dopamine conversion and decreases dopamine production in a dose-dependent manner while blocking receptor upregulation or hypersensitivity due to the administration of haloperidol [24]. Based on evidence showing that manic episodes are caused by the hypersensitivity of dopamine re-

ceptors, the reaction of the dopamine system to lithium may explain the mechanism of lithium's ability to treat bipolar disorder [25].

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is involved in neurotransmission via interneuronal synapses in brain regions controlling mood, such as the striatum, globus pallidus, and cerebral cortex [26]. A retrospective study on patients with depression demonstrated decreased activity of glutamic acid decarboxylase, an enzyme involved in GABA synthesis that potentially reduces GABA activity [26]. In addition, the serum GABA level was low in patients with depression, whereas an increased level was correlated with the treatment response to valproate in patients with manic episodes [27,28]. Long-term administration of a mood stabilizer to patients with bipolar disorder reduced the GABA turnover rate, reinforced GABA neurotransmission [29], upregulated GABA receptors in the frontal cortex and hippocampus, and downregulated GABA receptors in the hypothalamus [30,31]. In a different study, the administration of lithium or valproate reinforced the effects of GABA [32].

NEUROENDOCRINE SYSTEM

Hypothalamic-pituitary-adrenal Cortex Axis

Increased activity of the hypothalamic-pituitary-adrenal (HPA) cortex axis is a characteristic response to stress in mammals. Abnormal HPA axis activity is observed in psychiatric illnesses, including major depressive disorder. Overactivity of the HPA axis, such as increased corticotrophin-releasing hormone activity, has been reported in bipolar disorder [33], which may be associated with mixed manic episodes or depressive episodes more than with typical manic episodes [34]. In addition, the HPA axis abnormality in bipolar disorder is supported by the association between neuroendocrine abnormality and the severity of symptoms as well as between cortisol levels and the degree of anxiety, insomnia, or depression [34].

Furthermore, chronic stress can cause hippocampal atrophy, specifically atrophy of CA3 nerve cells as observed in a high glucocorticoid concentration environment. This indicates the HPA axis plays an essential role in hippocampal atrophy when subjected to stress. Stress and glucocorticoids may cause atrophy directly or reduce

cellular resilience by exposing vulnerable cells to various types of stimuli, such as ischemia, hypoglycemia, and excitatory amino acid toxicity. In addition, the HPA axis may be involved in the reduced brain-derived neurotrophic factor (BDNF) expression caused by chronic stress. In previous studies, attempts were made to mitigate the symptoms of bipolar disorder by reducing the level of HPA activation. Administration of mifepristone (RU-486), a glucocorticoid receptor (GR) antagonist, caused a small but significant decrease in HPA activity, suggesting a potential treatment for bipolar disorder [35].

Gonadal and Thyroid Hormones

Gonadal hormones can trigger the development of mood disorders and are associated with the clinical stage of mood disorders. The incidence of major depression and frequency of depressive episodes are higher in females than males, although the prevalence is similar between the sexes. Gonadal hormones contribute partly to the sex differences in symptoms. Estrogen activates serotonin signaling for antidepressant activity by influencing various neurotransmitters such as noradrenaline, dopamine, and GABA. Estrogen is also involved in neuroplasticity by increasing BDNF expression and intercellular signaling by protein kinase C (PKC) [36,37].

The association between thyroid hormones and mood disorders is well known. Administration of thyroxine and triiodothyronine (T3) is useful for treatment-resistant depression or bipolar disorder because the degree of thyroid activity is associated with the prognosis of bipolar disorder. Furthermore, thyroid hormones have neurotrophic effects. The T3-receptor complex can increase the expression of transcription factors or proteins responsible for intracellular signaling [38,39]. Thyroid hormones increase the level of cAMP response element-binding protein (CREB) and exert neurotrophic effects [40].

INTRACELLULAR SIGNALING

Theories have been proposed regarding the changes in neurotransmitters and neuroendocrine systems that partly explain the pathophysiological mechanisms of mood stabilizers and antidepressants in treating bipolar disorder. However, these theories need further validation. For example, the monoamine hypothesis does not explain why the clinical manifestations following administration of a

mood stabilizer appear after only several weeks; neurotransmission and neuroendocrine system activity can change depending on the stage of depression or manic episodes but not of bipolar disorder [41]. In addition, new models are needed to explain periodicity, a clinical finding characteristic of bipolar disorder, as well as various clinical manifestations. Changes in the intracellular signal transduction system, including second messengers, are currently being investigated.

Changes in the Neuronal Membrane

Na-K ATPase plays a role in maintaining the electrochemical potential difference across the cell membrane by controlling intracellular ion concentrations. The Na-K ATPase concentration is decreased in the peripheral blood cells of patients with acute manic episodes but is increased intracellularly [42]. In rodent experiments, the characteristic activity of bipolar disorder increased or decreased in a dose-dependent manner after administering ouabain, a Na-K ATPase inhibitor. This change was associated with activation of the extracellular signal-regulated kinase pathway [43,44].

The barrier functions and permeable features of a cell membrane change depending on the location and phospholipid concentration. Experiments using nerve cells are limited, and red blood cells or platelets are frequently used to study intracellular signaling because they share similar characteristics with neuronal cell membranes [45]. In patients with bipolar disorder, the hydrophobic region in the cell membranes of red blood cells and lymphocytes is altered [46], and the phosphatidylcholine concentration is not within the normal limits in patients with schizophrenia and manic episodes [47].

G-proteins

Most neurotransmitters or neuromodulators binding to G-proteins display particular intracellular effects. G-proteins consist of α , β , and γ subunits and stimulate/inhibit the Gs and Gi endoenzymes. Endoenzymes such as AC and phospholipase C adenosine generate secondary signaling molecules (cAMP and diacylglycerol, respectively). cAMP and diacylglycerol reactivate protein kinase A (PKA) and PKC, which phosphorylate matrix proteins to regulate metabolism or activate transcription factors. PKA is associated mainly with CREB, which activates the expression of various genes. PKC influences various signal-

ing systems, including the myristoylated alanine-rich C kinase substrate (MARCKS). Long-term clinical effects of antidepressants or mood regulators are hypothetically caused by secondary changes such as activation of various signaling systems and functional changes [48].

Gs/cAMP Signaling Pathway

The relationship between G-protein changes and the development of bipolar disorder have been investigated in previous studies. The peripheral blood cells in patients with bipolar disorder who did not receive medical treatment showed an increased level of a particular Gs α subtype but not Gs α mRNA, which indicates that Gs α only has an influence post-transcription [49,50]. In patients with manic episodes who did not take medication, the G-protein activity was increased in white blood cells, and in bipolar depressive episodes, both the Gs α and Gi α levels were decreased in white blood cells [51,52].

In a postmortem study, AC activation associated with Gs α was reportedly increased in the temporal and occipital lobes, influencing intracellular signaling via cAMP in patients with bipolar disorder [53]. Furthermore, the cAMP response to the β adrenaline stimulus was decreased in depressed patients, and cAMP production caused by the forskolin stimulus in the temporal and occipital lobes was increased [54,55].

Changes in the PKA level may reflect the increased cAMP activity in patients with bipolar disorder. A decreased level of the regulatory subunit of PKA was observed in the postmortem brain [56]. In a previous study, the PKA catalytic activity in the temporal cortex was reportedly enhanced in patients with bipolar disorder [57]. A different study suggested that abnormal cAMP-stimulated endogenous phosphorylation is due to cAMP stimulation in the platelets of patients with stabilized bipolar disorder [58,59].

PKA activation is affected by mood change inducers, electroconvulsive therapy, and mood stabilizers [60]. In the ground state with no stimulation, lithium prevents Gi α from binding to AC, increasing cAMP production. In contrast, when cAMP accumulates due to Gs α binding to AC caused by β -adrenaline stimulation, lithium induces separation of Gs α from AC and inhibits cAMP accumulation [61]. This bilateral reaction of lithium to cAMP indicates that lithium could have therapeutic effects on both manic and depressive episodes in bipolar disorder. In addition,

the increase in PKA activity observed in the postmortem temporal lobe is similar to the cAMP increase seen after lithium treatment [62].

Phosphatidylinositol Pathway

In the phosphatidylinositol (PI) pathway, $G\alpha_q/11$ controls phosphoinositol to influence intracellular signaling similar to $G_s\alpha$ control of cAMP via AC. In a postmortem study of bipolar disorder, the $G\alpha_q/11$ activity in the occipital lobe was reduced; however, $G\alpha_q/11$ binding was increased in the frontal lobe [63,64]. In addition, an increased PI 4,5-bisphosphate level was found in platelet cell membranes of a patient with manic episodes, indicating a significant increase in PI pathway activity during manic episodes [65,66]. Furthermore, the level of inositol monophosphatase, an enzyme forming the myo-inositol precursor of the PI pathway, was normal in patients with bipolar disorder, but the myo-inositol level was low [67].

In a postmortem study of patients with bipolar disorder, normal phospholipase C function was reported in the frontal, temporal, and occipital cortices. Conversely, PKC

activity in the platelet cell membrane was increased more in patients with manic episodes who were not medically treated than in healthy controls or patients with schizophrenia [68,69]. Another postmortem study reported increased PKC activity and α , γ , and ϵ PKC isozyme activities and decreased ϵ PKC level in the frontal cortex [70]. Mood stabilizers normalized the increased PKC activity, as shown in previous studies in which various drugs influenced PKA [71].

Pharmacologically, lithium firmly controls inositol-1-phosphatase and polyphosphate 1-phosphatase, which play significant roles in the PI pathway [72]. Free inositol becomes depleted if these enzymes are inhibited. Consequently, the synthesis of constituent substances of the PI pathway is reduced, decreasing intracellular transmission [73]. Manic episodes can be considered hyperactivity of particular endoneurial functions, in which the mood-stabilizing effects of lithium should be similar to the characteristics in manic episodes. In addition, lithium alters the PI signaling pathway, modulates PKC-mediated pathways and gene expression, and induces long-term effects.

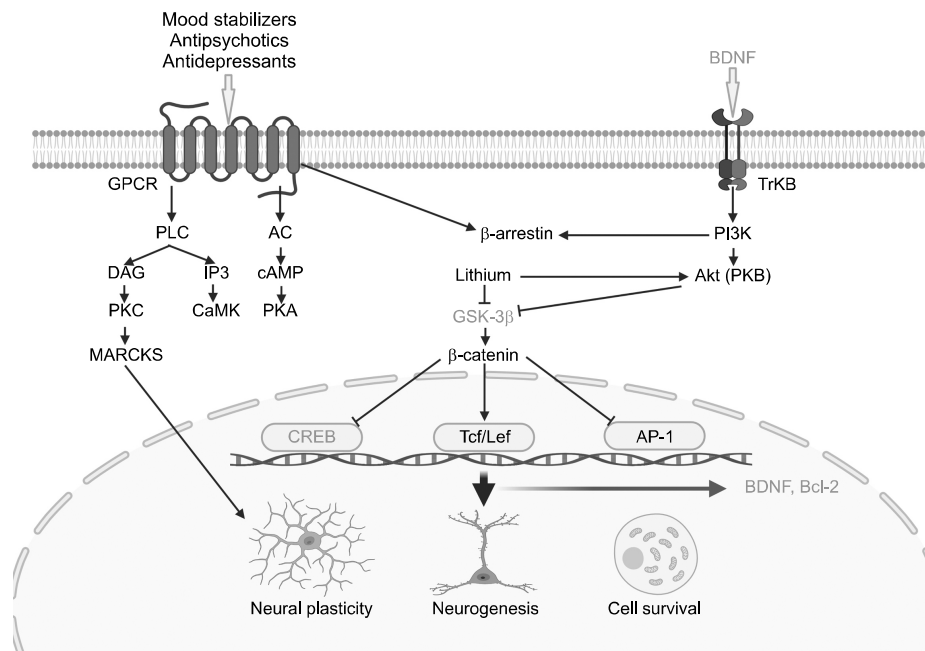


Fig. 1. Intrasignaling pathways as the mechanism of action for mood stabilizers, antipsychotics and antidepressants.

AC, adenylyl cyclase; AP-1, activator protein-1; BDNF, brain-derived neurotrophic factor; CaMK, Ca^{2+} /calmodulin-dependent kinase; cAMP, cyclic adenosine-3',5'-monophosphate; CREB, cAMP-responsive element binding protein; DAG, diacylglycerol; GPCR, G protein-coupled receptor; GSK-3 β , glycogen synthase kinase-3 β ; IP3, inositol 1,4,5-triphosphate; MARCKS, myristoylated alanine-rich C-kinase substrate; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; TrkB, tropomyosin receptor kinase B.

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Reportedly, long-term lithium administration decreased the concentrations of cytoplasmic PKC- α and cell membrane PI 4,5-bisphosphate [72,73]. MARCKS is a PKC substrate participating in multiple intracellular processes involved in synaptic plasticity. In a previous study, 4 weeks of lithium administration resulted in significantly decreased MARCKS expression in the hippocampus [73]. In addition, PKC activity was reported to play a vital role in the ability of lithium to act as a transcription factor (Fig. 1) [74].

Furthermore, lithium and valproate show efficacy in bipolar disorder, and both act on PKC despite their different molecular structures. Researchers have investigated the efficacy of selective regulators of PKC as a treatment for bipolar disorder. Tamoxifen, a PKC inhibitor, was proven as a potential treatment for manic episodes in animal studies. In the latest double-blind placebo-controlled clinical study involving subjects with manic episodes, tamoxifen showed excellent treatment effects equivalent to those of lithium and valproate [75,76]. Efforts to develop new drugs targeting PKC should continue.

The increase in the intracellular calcium level is additional evidence supporting the hypothesis that the PI pathway is hyperactivated in bipolar disorder. In patients with bipolar disorder who did not receive medical treatment, the baseline calcium concentration in the peripheral blood cells was increased [77]. In addition, the calcium response to stimuli was increased in patients who did not take medication, but reactivity decreased in stable patients who took lithium [78,79].

NEUROPLASTICITY

Recently, the effects of neuroplasticity and neuroprotection have been investigated in multiple studies. Neuroplasticity refers to a collective change in the brain's interactions with the environment in the neural network. Neuroplasticity includes synaptic remodeling, long-term potentiation, axon sprouting, synaptogenesis, and neurogenesis [80]. Neuroprotection refers to the mechanism preventing neuronal cell death due to harmful stimuli such as ischemia, free radicals, and excess glutamate.

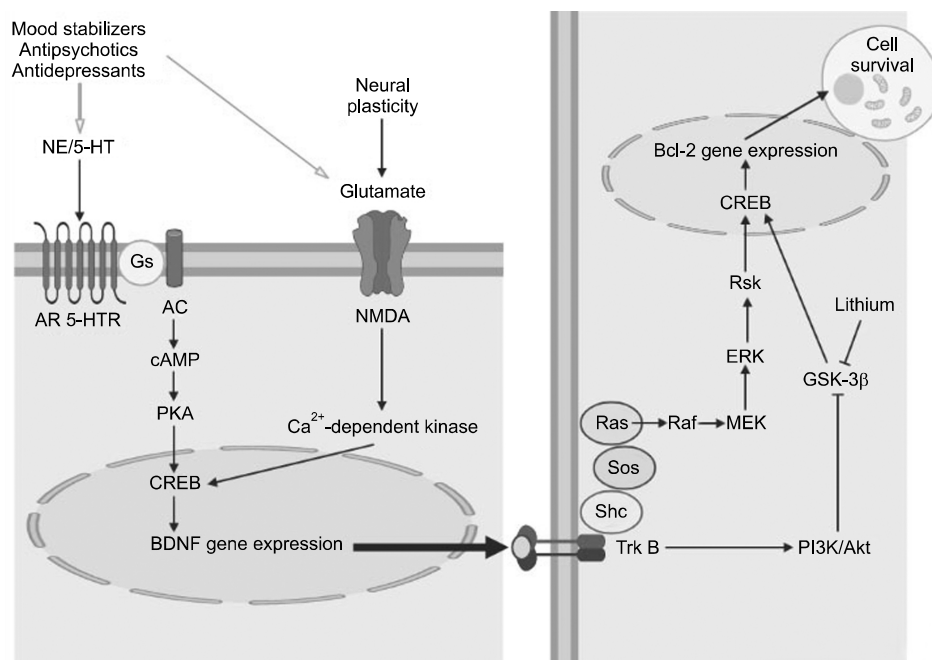


Fig. 2. Effects of mood stabilizers, antipsychotics and antidepressants on neuroplasticity through cell signaling systems.

5-HT, serotonin; 5-HTR, serotonin receptor; AC, adenylyl cyclase; AR, adrenergic receptor; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine-3',5'-monophosphate; CREB, cAMP-responsive element binding protein; ERK, extracellular signal-regulated kinase; Gs, G proteins; GSK-3 β , glycogen synthase kinase-3 β ; MEK, Ras/Raf/Mitogen-activated protein kinase (MAP)/ERK kinase; NE, norepinephrine; NMDA, N-methyl-D-aspartate receptor; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; Shc, Src homology and containing protein; Sos, son of sevenless; TrkB, tropomyosin receptor kinase B.

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Long-term administration of lithium can prevent neuronal apoptosis by blocking excitatory toxicity of N-methyl-D-aspartic acid [81], involving transcription factors such as CREB, neurotrophic factors such as BDNF, phosphorylation enzymes such as glycogen synthase kinase-3 (GSK-3), and mitogen-activated protein kinase (MAPK) (Fig. 2).

CREB

CREB is a transcription factor involved in long-term functional control of nerve cells by affecting the transcription of various genes or BDNF function. Antidepressants can upregulate CREB, lithium may decrease or increase CREB expression depending on the specific brain region [82-84], and valproate increases CREB expression in different brain regions [85].

BDNF

BDNF is a growth factor essential for the survival and functional maintenance of nerve cells. BDNF acts on TrkB receptors to activate the MAPK pathway and increases the expression of neuroprotective proteins such as Bcl-2 [86]. BDNF is a target of CREB; increased CREB and BDNF levels are observed after antidepressant treatment, similar to the behavioral changes in animal models of depressive behaviors. Furthermore, the BDNF level increases after electroconvulsive therapy, and the administration of BDNF has similar characteristics to those of antidepressant administration in animal studies. BDNF and various endogenous growth factors stimulate the MAPK pathway, increasing transcription and BDNF activity, which involve roles of lithium and valproate [87]. Polymorphisms in BDNF genes could influence the cognitive ability of patients with bipolar disease or their age of development, a topic that is currently being actively researched [88].

GSK-3

The GSK-3 enzyme that mediates various intracellular signaling pathways, significantly contributing to neuroplasticity and cell elasticity regulation. GSK-3 deactivates transcription factors or cytoskeleton-forming proteins by phosphorylation, acting on axonal microtubules and synaptic vesicle functions. GSK-3 activity promotes apoptosis, which is prevented by inhibiting GSK-3 [89,90].

In addition, GSK-3 activation is involved in hypoxia-induced apoptosis [90]. GSK-3 activity is inhibited by PKC

and BDNF, as mentioned above, controlling Bcl-2 protein expression via p53 and inhibiting transcription via CREB [87]. GSK-3 is involved in multiple signaling systems. Various growth factors, such as BDNF, have neuroprotective functions partly due to GSK-3. Therefore, GSK-3 inhibitors may be therapeutic for bipolar disorder; lithium and valproate can inhibit GSK-3 [91]. The capability of atypical antipsychotic drugs, such as olanzapine, to inhibit GSK-3 was also shown (Fig. 1) [92]. Based on imaging studies, drugs such as lithium and valproate exert neuroprotective effects by acting on multiple intracellular signaling and gene transcription factors. In a patient with a family history of bipolar disorder, the prefrontal cortex volume was decreased by 40%. In patients with bipolar disorder who received long-term lithium treatment, a reduction in the prefrontal cortex volume was not observed (the volume was similar to that in normal controls) [93,94].

CIRCADIAN RHYTHM

The circadian rhythm of mammals is thought to be responsible for the suprachiasmatic nucleus. The circadian rhythm is involved in physiological controls such as mobility, the sleep–wake cycle, body temperature, and hormone secretion. Circadian rhythm dysregulation may be associated with the development of mood disorders such as bipolar disorder and clinical features related to disease periodicity [95]. The relationship between the circadian rhythm and bipolar disorder was confirmed in animal models and human studies; the sleep cycle was delayed in patients with type 1 bipolar disorder [96], but the delay may have been caused by the patients' drug treatments. Furthermore, the appearance of circadian rhythm changes was confirmed in human patients in the clinical setting. In addition, sleep deprivation resulted in therapeutic effects in unipolar or bipolar depression but caused manic episodes in patients with bipolar disorder [97,98]. A change in the sleep cycle may be associated with dopamine receptors in the brain. In another study, sleep deprivation increased the expression of genes associated with neuroplasticity [99].

In addition, various clock genes, including CLOCK, BMAL1, mPer1, mPer2, mPer3, mTim, mCry1, and mCry2, play vital roles in circadian rhythm control. Circadian rhythm genes are implicated in the sensitiza-

tion mechanism of cocaine-induced behaviors, a typical bipolar disorder model [100]. In addition, in mPer1 and mPer2 mutant mice, behaviors such as conditioned place preference were increased or decreased, and these behaviors were shown to be controlled by clock genes. Lithium may induce a phase delay in the circadian rhythm and extend the rhythm cycle by acting directly on suprachiasmatic nucleus cells [101].

EPIGENETIC MECHANISMS

Among the mechanisms that can cause long-lasting protein expression and functional changes, epigenetics has been the focus of the latest research because of its influence on the pathophysiology of depression and mood disorders [102,103]. Epigenetic changes include DNA methylation, which alters DNA covalent bonding, translational repair after acetylation or methylation of the histone N terminal, and transcriptional gene expression [102,103]. A long-term epigenetic change can explain some phenomena in depression that have been difficult to understand otherwise. Examples that can be explained by epigenetic changes include the following: a difference in the incidence of depression development in monozygotic twins, different depressive symptoms in an inbred rodent animal model, chronic recurrence of depression in women, and a higher prevalence of depression in women [104].

An epigenetic change is an alteration in genetic function subject to environmental influences with no modification of the DNA sequence. Epigenetic changes can explain the inconsistent results of previous depression studies. The influence that DNA sequence polymorphisms exert on depression pathophysiology may not be substantial. Despite the involvement of epigenetic changes in mental disorders, only two classes of chromatin modification processes have been investigated. The first is DNA methylation, which plays an important role in how the behavior of the mother influences her children's emotional development and adult behavior. In mouse pups who did not breastfeed well and thus did not receive appropriate care, anxiety behavior increased when the pups became adults compared with pups who received sufficient maternal care. In addition, GR expression was decreased in the hippocampus. A decrease in GR expression is caused by increased methylation of the GR gene promoter. How-

ever, a long-lasting molecular wound that occurs during the first week of life can be repaired simply by maternal care such as good licking and grooming [105]. The increase in methylation was attenuated after administration of a histone deacetylase inhibitor. The second chromatin modification process is histone acetylation, which involves activation of protein transcription and chromatin relaxation, and histone acetylation is thought to play an essential role in the action of antidepressants. Improving histone acetylation at the BDNF gene promoter in the hippocampus may cause depressive symptoms in socially discouraged subjects. Histone acetylation inhibitors showed effects similar to those of antidepressants in studies investigating social discouragement and other behaviors [106]. Researchers are currently attempting to elucidate diverse information regarding chromatin regulatory proteins and genes. Before these research findings are used to treat patients, clinicians should be aware that these results were obtained from *in vivo* experiments and not human studies. However, the findings indicate a possible association between local chromatin and the antidepressant treatment response in depression.

CONCLUSION

In summary, the neurobiological etiology of bipolar disorder is multifactorial. However, it can be estimated from an integrated point of view that mood episodes, treatment responses, and medical diseases resulting from the sequelae of bipolar disorder might be originated from the neuromolecular pathophysiology of bipolar disorder.

Improved understanding of bipolar disorder can only be attained by continued research efforts on the neurobiology of bipolar disorder. Molecular clock gene dysfunction appears repetitively in bipolar disorder, and circadian gene dysfunction occurs both when a mood disorder episode occurs and during the remission of signs and symptoms. Future studies should be performed to determine how circadian gene abnormalities are modified, facilitating the modification of gene abnormalities to control mood. In addition, discovery of proteins and genes associated with neuroplasticity is important to create novel applications for mood control. Finally, identifying the neurobiological etiology of bipolar disorder can aid customized treatment or targeted therapy development.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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