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Glial Pathology in Bipolar Disorder: Potential Therapeutic Implications

Xiao-Hua Dong[1,2] & Xue-Chu Zhen[1]

1 Jiangsu Key Laboratory for Translational Research for Neuropsycho-Diseases, Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, Suzhou, Jiangsu, China
2 Department of Pharmacology, College of Pharmacy, Hebei North University, Zhangjiakou, Hebei, China

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Correspondence
X.-C. Zhen, Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, 199 Ren'ai Road, Suzhou, Jiangsu Province, China.
Tel.: +86-512-65880369;
Fax: +86-512-65880369;
E-mail: zhenxuechu@suda.edu.cn
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SUMMARY

Bipolar disorder (BD) is a chronic and severe mental disorder with recurrent episodes of mania and depression. In addition to neuronal alterations, accumulating evidences have revealed the importance of glial system in pathophysiology and phenotype of the illness. Postmortem studies have repeatedly demonstrated the alterations in glial cells and its functions in patients with BD. The activated microglia and inflammatory cytokines are proposed to be the potential biomarkers that may help to predict disease exacerbation in BD. On the other hand, anti-BD drugs have been shown to produce profound effects on glial activity, which not only contributes to the therapeutic efficacy, but may also provide a potential target for the drug development of BD. We will focus on the recent development of glial abnormalities and potential therapeutic benefits targeted to glial modulation in BD.

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Introduction

Bipolar disorder (BD) is a devastated psychiatric disorder, and the etiology of BD remains largely unknown. It is generally believed that the complex interactions between genes and environment attribute to the pathogenesis of the disease [1–3]. Although the abnormal neurotransmission, particularly serotonin system disorder, is traditionally attributed to the mechanism of BD, recent information indicates that, in addition to neuronal system, glial activity also contributes to the BD pathology and the therapeutic response of anti-BD drug therapy.

Astrocyte, microglia, and oligodendroglia are family of glial system in the central nervous system. Astrocyte is the large stellate cell, and its roles are far beyond the traditionally recognized supporting function to neurons. Microglia is specialized macrophage, and oligodendroglia serves as neuronal satellite in gray matter and involves in myelin sheath formation in white matter. Homeostasis, support, and protection of neurons are largely dependent on glial cells in the brain. The importance of glial activity in the pathophysiology of neurodegenerative disorders, psychosis, and stoke is well documented [4–10]. Recently, accumulating evidences suggest a potential involvement of glial cells in the pathogenesis and pathophysiology. The postmortem studies of BD revealed glial cells were decreased significantly in the subgenual prefrontal cortex, particularly in patients with familial BD [11]. Furthermore, transcripts of astrocyte-specific glial fibrillary acidic protein (GFAP) in the anterior cingulate cortex were reported to decrease significantly in white matter in patients with BD [12]. The decreased expression in frontal cortical GFAP was further confirmed later [13]. In addition to the changes in astrocytes, microglial activation, and oligodendrocyte dysfunction in the pathological development of BD, we will focus on the BD-specific glial pathology and potential therapeutic role for modulating glial activity in the illness.

Glial Pathology in Bipolar disorder

Microglia Activation in BD

Microglia is a resident macrophage of the brain, which is activated in response to changes in environment such as stress and insult by regulating cytokine production, neuronal plasticity, and neurotransmission [14,15]. Upon activation, microglia can produce either neurotoxic or neuroprotective effects depending on the polarization status. M1 polarization enables microglia to produce proinflammatory cytokines such as TNF-α and IL-1β, which potentially could injure neurons, whereas M2 polarization can increase the production of neurotrophic factors and antiinflammatory factors that are beneficial for the repairing of damaged neuronal tissues [14–16]. Accumulating evidences indicate that some of

the cytokines such as TNF, IL-1, IL-2, and IL-6 are significantly changed in patients with BD [15–21]. The serum TNF-α level is higher in acute episodes of the illness, which is responsive to the anti-BD drug treatment [21]. Although the precise role of inflammatory response in the pathophysiology of the BD remains largely unknown, it was proposed that activated microglia may serve as a possible biomarker for predicting disease exacerbation and as a measure of pharmacological response in BD therapy.

Alteration of Serum S100B in BD

S100B, a protein produced by astrocyte and oligodendrocyte, can bind to calcium and modulate various cellular responses along with the calcium signal transduction pathway [22]. It regulates intracellular signal transduction that is related to energy metabolism, cell-to-cell communication, and cell growth [23]. The genetic variability within the S100B gene indicated that it may be a susceptibility gene for BD [24]. It was reported that decreased S100B immunopositive astrocytes and oligodendrocytes were found in CA1 area of hippocampus in patients with BD [25]. S100B protein can be easily measured in human serum, which renders it may be a valuable index for glial activation in response to various conditions. In fact, elevated serum S100B is a common finding in neuropsychiatric disorders, such as schizophrenia and major depression [26]. Early study showed that serum S100B was elevated in patient with first manic episodes [27]. This finding was confirmed by other studies in both depressive and manic episodes of the disease, and moreover, lithium treatment could effectively reverse the levels of S100B [28,29]. These clinical observations were also confirmed in experimental study using ouabain-induced rat model of mania [30]. However, a very recent follow-up study reveals some dynamic changes in S100B in bipolar offspring: normal during adolescence but increased during adulthood. These changes are independent of psychopathologic state of the offspring. This is interesting, and it may implicate that S100B may not have predictive value for the BD [31].

Oligodendrocyte Dysfunction in BD

Oligodendroglias are known to serve as neuronal satellites in gray matter and form myelin sheaths in white matter. Myelin provides the structure importance for rapid impulse conduction in the nerve system. Decreased gray matter volume in BD and schizophrenia has been repeatedly reported [32]. A further study reveals the linear correlation between decreased gray matter volume in the dorsolateral frontal cortex and number of manic episodes of BD [33]. In addition, a significant alteration in white matter was also found in BD [34]. BD-associated deficits of oligodendrocyte/myelin gene expression by microarray and quantitative real-time PCR studies found that many genes, including PLP1, MBP, and CLDN11, were downregulated in postmortem frontal cortices of patients with BD [35]. Decreased number of oligodendrocytes has also been observed in BD using optical dissector method [36]. Moreover, electron microscopic study revealed ultrastructural signs of apoptosis and necrosis of oligodendrocytes in the prefrontal cortex and the caudate nucleus of patients with BD [37]. ErbB, an important molecule in regulating the structure and functions of oligodendrocytes, is genetically linked to neuropsychiatric disorders including schizophrenia and BD. Loss of ErbB signaling in oligodendrocytes results in the decreased myelin thickness and slower conduction velocity in brain axons, which is a potential mechanism for BD [38]. Thus, it is conceivable that decreased oligodendrocytes and gray matter volume will lead to atrophy of neurons that will ultimately change the prefrontal network function, giving the importance of the brain area in the modulation of emotion and cognition [39].

Potential Medication Target of Glial Cells in BD Therapy

Lithium (Li^+), valproic acid (VPA), and carbamazepine (CBZ) are the three classical antibipolar disease drugs. As a mood stabilizer, Li^+ has been used to treat BD for more than 60 years [40]. The molecular mechanism of mood stabilizer such as lithium is suggested to associate with alteration in inositol phosphate/phospholipid signaling and glycogen synthase kinase-3β (GSK-3β), although other pathways may be also involved [41,42]. Given the important roles of glial system in the regulation of neurotransmitters, synaptic efficacy, blood–brain barrier, and trophic support of neurons in normal brain functions and in pathophysiology in BD as described above [43], increased attention has been paid to the effects of those mood stabilizers on glial systems and to explore the potential approach targeted to glial therapy for BD. It seems that antibipolar drugs elicit broad spectrum of effects on glial functions that may, in turn, contribute to the therapeutic mechanism of drugs.

Inhibition of Astrocytic Glycogen Synthesis and Promotion of Intracellular Alkalinization

Glycogen in the adult brain is largely stored in the nonneuronal cells, particularly astrocytes, and actively metabolized and used as a store of energy resource for the demands of neurons [44]. Treatment of primary astrocytes, with 1 mM lithium, markedly reduced the steady state of glycogen content, which is attributed to the inhibition of phosphoglucomutase (PGM) and dephosphorylation of glycogen synthase [45]. Altered PGM activity is also reported in BD patients with lithium treatment. Interestingly, the peripheral PGM expression in leukocytes or erythrocytes of patients with BD in response to lithium treatment was not altered, which could be the result of compensatory response as suggested by Csutora et al. [46].

Clinical studies with MRS revealed a change in cerebral pH in patients with BD [47,48]. Chronic antibipolar drug treatment can cause progressive intracellular alkalinization in astrocytes. Intracellular alkalinization inhibits myo-inositol uptake and leads to the suppression in inositolphosphate/phospholipid signaling. It seems that antibipolar drugs elicit intracellular alkalinization in astrocytes through distinct mechanism. Chronic treatment of lithium increases astrocytic pH value by stimulating Na^+/H^+ exchanger (NHE). The alkalosis is a gradually developing process, and thus, the substantial decrease in cellular myo-inositol content may require a relatively long time, which is in line with the delayed therapeutic response for antibipolar drug treatment [49].

Chronic treatment to astrocytes with therapeutically relevant concentrations of either CBZ or VPA also increased pH value [50]. This alkalinization is associated with the increased activity of NBCe1, a subtype of Na^+/HCO_3^- cotransporters (NBCe) and the major acid-extruding HCO_3^--dependent transporter in glial cells. Astrocytic alkalinization not only inhibits inositolphosphate/phospholipid signaling and intracellular Ca^{2+}, but also upregulates the expression of Ca^{2+}-dependent phospholipase A_2 [51]. It is believed that intracellular alkalinization in astrocytes is one common therapeutic mechanism of the three antibipolar drugs.

Modulating the Production of Astrocytic Neurotrophic and Neuroprotective Effects

Brain-derived neurotrophic factor (BDNF) is widely expressed in the adult brain and plays an important role in neurogenesis and neuroplasticity. Decreased serum BDNF was reported in both the manic and depressive phases of patients with BD [52,53]. Conversely, another report revealed increased serum BDNF in the bipolar manic state [54]. Thus, alterations of BDNF in the peripheral blood of patients with BD are not always consistent and may depend on the state or the phenotype of the illness. A recent study demonstrated that VPA, but not lithium treatment, enhanced glial cell-derived neurotrophic factor (GDNF) and BDNF expression in astrocytes via modulating the activities of histone modifications and/or transcription factors [55]. The roles of antibipolar drug-regulated production of neurotrophic factors and its potential contribution to the drug efficacy remain to be fully elucidated.

Tissue plasminogen activator (tPA) is expressed in several regions of brain and plays regulatory roles such as neurite outgrowth and synaptic plasticity. tPA is regulated by plasminogen activator inhibitor-1 (PAI-1), the endogenous inhibitor of tPA. Binding of PAI-1 to tPA terminates tPA enzymatic activity. It is interesting to note that VPA treatment down-regulated PAI-1 activity and thus led to enhanced tPA activity in astrocyte [56]. The regulatory effects of anti-BD drugs on PAI-1/tPA are still not fully explored. How the drug-regulated tPA/PAI-1 activity in astrocyte contributes to the drug's therapeutic effect of BD is worth further study.

Regulation of Astrocytic FEZ1 Expression

The microarray study has found that treatment of respective anti-BD drugs such as lithium, VPA, CBZ, and lamotrigine differentially altered the expression pattern of genes, while fasciculation and elongation protein zeta 1 (FEZ1) in human astrocyte-derived cells is the only gene induced by all four mood stabilizers [57]. FEZ1 protein was expressed in the cytoplasm of both transformed and primary astrocytes, as well as in neuronal cells. FEZ1 is involved in the extension and maintenance of astrocytes processes, mitochondrial functions, and the development and maintenance of structural formations. In addition, FEZ1 has been reported to play an important role in the establishment of neuronal polarity by controlling the axonal transport [58,59]. Mitochondrial dysfunction in BD is well recognized [60,61], and antibipolar drugs modulate the FEZ1 expression and improve mitochondrial function, which may provide a potential therapeutic benefit for BD.

Regulation of Synaptic Activity and Neuronal Excitability via Astrocyte

Kainate receptors are widely distributed in the central nervous system both in neurons and astrocytes, and actively involved in the regulation of synaptic activity [62]. Chronic treatment with antibipolar drugs such as carbamazepine, valproic acid, or Li^+ selectively suppressed mRNA and protein expression of GluK2 in astrocytes, but not in neurons [63]. GluK2 activation increases intracellular Ca^{2+} in astrocyte, thereby promotes Ca^{2+}-dependent release of "gliotransmitters", such as glutamate and ATP [64,65], and consequently enhances the efficacy of glutamatergic synaptic activity. Thus, downregulation of GluK2 expression in astrocytes by antibipolar drug treatment may provide a potential mechanism for drug's effects [66]. The selective effect of antibipolar drugs on astrocytic expression of GluK2 may also suggest a potential target for anti-BD drug discovery.

VPA is able to modulate the synaptic excitatory/inhibitory (E/I) balance. It is known that cell adhesion molecules (CAMs) and extracellular matrices (ECMs) are involved in the formation and maturation of synapses and the synaptic E/I balance [67,68]. VPA has been found to increase the mRNA levels of two excitatory postsynaptic CAMs (neuroligin-1 and neuregulin-1) and ECMs (neuronal pentraxin-1 and thrombospondin-3) in primary rat astrocyte cultures, but not in neurons, in a time- and concentration-dependent manner [69].

Na^+, K^+-ATPase is a membrane-bound enzyme enriched in both neuron and astrocyte and is important for neuronal excitability [70]. This enzyme is involved in the regulation neuronal electrochemical gradients by active exchange of Na^+ and K^+. Lowered brain Na^+, K^+-ATPase density was found in patients with BD [71]. Chronic administration of lithium or carbamazepine to mice altered mRNA expression of the Na^+, K^+-ATPase (especially $\alpha 2$ and $\beta 1$) in both neurons and astrocytes, and increased Na^+, K^+-ATPase activity [72]. Whereas acute carbamazepine or lithium treatment has no effects to Na^+, K^+-ATPase activity [73], which is in agreement with the time lag of effectiveness for antibipolar drug therapy.

Taken together, antibipolar drugs modulate synaptic activity and neuronal excitability through multiple mechanisms, which include GluK2 expression, synaptic E/I balance, and Na^+, K^+-ATPase activity.

Conclusions

Mounting evidences support the phenomenon of glial abnormalities in bipolar disorder. It appears that structural or functional alterations for three main types of glial cells including microglia, astrocyte, and oligodendrocyte contribute to the pathophysiology in BD. The pharmacological mechanisms for antibipolar treatment are concerned with the regulation of glial functions. No doubt, these progresses will contribute to our understanding in the pathophysiology of BD. Given the importance of glial abnormalities in bipolar disorder, glial cells may pave a potential pathway for future BD drug discovery.

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Conflict of Interest

The authors declare no conflict of interest.

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