Chapter 23

Bipolar disorder and plasticity: a key target for new treatment

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23.1 Introduction

Despite detrimental effect of bipolar disorder (BD), large proportion of patients with BD still do not experience sufficient treatment response leading to significant impairment in everyday functioning. Countless attempts have been taken for deciphering the neurobiology of BD and developing new therapeutic targets. However, "an oldie but a goodie" lithium is still the most effective pharmacological agent for BD (Won & Kim, 2017). Despite its confirmed treatment effects, lithium's exact mechanism of action in mood regulation is still yet to be clarified. Along with the direct inhibition on glycogen synthase kinase 3 (GSK-3), increasing studies highlight lithium's various effects on neurotrophic factors, neurotransmitters, oxidative metabolism, apoptosis, neuronal structures and glia, and second messenger systems which all are important factors contributing to plasticity of brain (Machado-Vieira, 2018; Wada, 2009). The evidence of disturbed plasticity in patients with BD is evident in both cellular and anatomical level. This chapter will elaborate current evidence for the dysfunction plasticity in BD, with a particular focus on the target for treatment.

23.2 Concepts of plasticity and implications in bipolar disorder

Plasticity, defined as ability to undergo and sustain change, is essential for the proper functioning of our nervous system by allowing organisms to maintain homeostasis to external change (de Sousa et al., 2014). Neuroplasticity refers to change of synaptic number and strength alternation, remodeling of axonal and dendritic architecture, growth of neuronal cell body, and generation of new neurons (in some parts of brain) (Sweatt, 2016). Synaptic

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plasticity is a more specific term within neuroplasticity which refers to ability of synapses to strengthen or weaken over time, in response to increases or decreases in their activity (Fig. 23.1) (Citri & Malenka, 2008). Impairment of neuro- and synaptic plasticity involving dysregulation of neurotrophic factors and proteins are associated with BD while activation of neuroprotective and neurotrophic pathways are linked to the therapeutic effects of mood stabilizers (Soeiro-de-Souza et al., 2012). Lithium, which is considered as a "gold standard mood stabilizer," is known to exert its effect via regulating neurotrophic factors, MAPK, Bcl-2, phosphoinositol signaling, intracellular calcium, glutamate activity, and GSK-3 which all lead to enhanced neuroplasticity.

23.3 Cellular studies

23.3.1 Mitochondrial-mediated pathway

In cellular level, studies showed that patients with BD have lower volume, decreased density, and smaller number, and reduced size of neurons and glial cells involving limbic regions including subgenual prefrontal cortex (PFC), orbital cortex, dorso-lateral PFC, amygdala, and basal ganglia (Cotter, Pariante, & Everall, 2001; Manji & Duman, 2001). Consistent studies reported mitochondrial dysfunction and associated dysregulation of calcium cascade as one of the most important biological abnormalities reported in BD (de Sousa et al., 2014). Mitochondria is important not only in regulating cellular energy metabolism but is also involved in modulation of cellular calcium levels, production of free radicals, and regulation of apoptosis. Thus it inevitably plays important role in neural plasticity and cellular resilience (Cheng, Hou, & Mattson, 2010). In the intrinsic mitochondrial-mediated

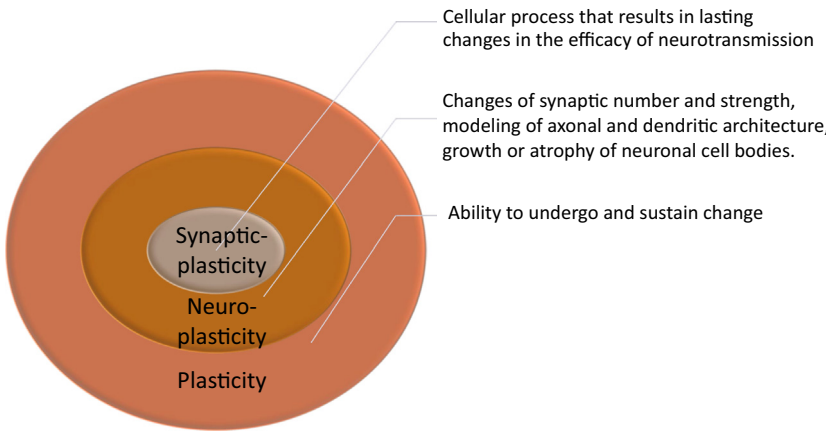

FIGURE 23.1 General concept of plasticity (de Sousa et al., 2014).

pathway, activation of proapoptotic BCL-2 family and heightened cytoplasmic calcium may enhance neuronal cell death and synaptic damage (Youle & Strasser, 2008). Likewise, BCL-2 family is also involved in facilitation of axonal regeneration, neurite growth, neuronal survival, and neurogenesis (Vinet, Bernier, & Parent, 2002). A polymorphism of BCL-2 antiapoptotic gene (rs956572) was found to be associated with an abnormal BCL-2 expression and dysfunctional calcium homeostasis in lymphoblastoid cells from patients with BD (Machado-Vieira et al., 2011). Another study reported that rs956572 polymorphism was related with increased levels of glutamate in anterior cingulate cortex of patients with BD (Soeiro-de-Souza et al., 2013).

Studies further showed that mitochondrial-mediated pathway involving BCL-2 and calcium regulation might be a promising therapeutic target. Chronic lithium therapy was shown to prevent oxidative stress and loss of mitochondrial membrane by blocking increment of calcium (Tseng & Lin-Shiau, 2002). In addition, lithium might reverse BCL-2 polymorphism (rs956572) associated dysfunctional calcium in BD (Yucel et al., 2007). Moreover, Bcl-2 expression and protein levels in the frontal cortex, hippocampus, and striatum were enhanced after long-term lithium therapy (Chen et al., 1999; Manji, Moore, & Chen, 1999). Likewise, electroconvulsive treatment, which is known to have a rapid mood stabilizing effect, is reported to increase BCL-2 expression leading to increased precursor cell proliferation in the dentate gyrus DG (Perera et al., 2007; Soeiro-de-Souza et al., 2012).

23.3.2 Neurotrophic factors and associated pathway

In terms of neurotrophic signaling cascade, brain-derived neurotrophic factor (BDNF) and its related pathway are known to play important roles in the pathophysiology of BD (Bramham & Messaoudi, 2005). BDNF binds to tyrosine kinase B receptor (TrkB) and activates downstream pathway involving phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) signaling pathway and extracellular regulated kinase (ERK)−mitogen-activated protein kinase (ERK/MAPK) pathway. BDNF itself is important for neurogenesis, neuronal survival, and normal maturation of neural development pathways. Moreover, it is important for synaptic plasticity, dendritic growth, and long-term memory consolidation (Post, 2007). Studies suggested that BDNF serum levels are decreased in depressive and manic episodes, which returned to normal levels in euthymia (Cunha et al., 2006; Machado-Vieira et al., 2007). The BDNF level was also shown to be negatively correlated with severity of manic and depressive symptoms (Fernandes et al., 2009). BDNF Val66val polymorphism was associated with increased risk of rapid cycling (Muller et al., 2006) while patients with BDNF val66met polymorphism

responded better to lithium prophylaxis than other genotype (Rybakowski et al., 2005).

The ERK/MAPK pathway is a major intracellular signaling cascade controlling the biological effects of neurotrophic factors and long-term cell plasticity (Chen & Manji, 2006). In the ERK/MAPK pathway, ribosomal S6 kinase is enhanced which activates cAMP response element-binding (CREB) protein (Sakamoto, Karelina, & Obrietan, 2011). CREB plays an important role in expression of the neuroprotective proteins, and this pathway is activated when BDNF binds to TrkB, which is known to be abnormal in patients with BD (Einat & Manji, 2006). PI3K also plays an important role in regulation of cell apoptosis, metabolism, and survival. The PI3K induces phosphoinositide dependent protein kinase-1 activating Akt serine/threonine kinase (Matsuda et al., 2019). The lowered PI3K/Akt signaling pathway eventually results in abnormalities of neuroplasticity.

Multiple studies suggested that BDNF and its related downstream pathway could be a potential therapeutic target of BD. BDNF is closely associated with the mechanism action of not only mood stabilizers but also antidepressants (Castren & Rantamaki, 2010; Coyle & Duman, 2003). For example, blockage of BDNF signaling with either a TrkB inhibitor or ERK/MAPK pathway inhibitor decreased the effects of antidepressants (Saarelainen et al., 2003). Likewise, long-term therapy with lithium and valproate increased BDNF concentration in hippocampus and PFC (Frey et al., 2006; Grande et al., 2010). Chronic lithium and valproate treatment were also found to activate ERK/MAPK pathway (Yuan et al., 2001) and they were also known to increase the levels of activated ERK in the emotion related brain lesions including anterior cingulate cortex and hippocampus in mice model (Chuang et al., 2002).

23.3.3 Glycogen synthase kinase-3β

GSK-3 of mammals has two isoforms, GSK-3α and GSK-3β, and they are associated with the regulation of glycogen synthesis in response to insulin (Wada, 2009). The difference arises from phosphorylation of tyrosine 279 and 216 for GSK-3α and GSK-3β, respectively. Although cerebral GSK-3α is known to be involved in neurodevelopment, no studies to date has reported importance of GSK-3α in the pathophysiology of major neuropsychiatric disease including BD (Dandekar et al., 2018). In contrast, GSK-3β is a key regulator of apoptosis, cellular plasticity, and resilience of neurons (Adli et al., 2007; Dandekar et al., 2018). The relationship between GSK-3β gene polymorphism and symptom severity of patients with mood disorders including BD and major depressive disorder (MDD) were repeatedly shown.

The role of GSK-3β in the pathophysiology of BD was discovered rather serendipitously from study results of lithium and valproate showing selective inhibitors of GSK-3β (Adli et al., 2007; Valvassori et al., 2017). Grimes and

Jope proposed that GSK-3β acts like a "gatekeeper" over a numerous downstream transcription factors and pathways which all play important role in regulating neuroplasticity (Grimes & Jope, 2001). The advantage of targeting GSK-3β is that GSK-3β is closely associated with mitochondrial-mediated pathway involving BCL-2, ERK/MAPK pathway, and PI3K/Akt signaling pathway (Soeiro-de-Souza et al., 2012; Soeiro-de-Souza et al., 2013). Disinhibition or increased activity of GSK-3β can directly cause decreased level of β-catenin resulting in lowered BDNF and neuroplastic factors (Dandekar et al., 2018). The lowered BDNF and neuroplastic factors in turn will cause lowered activities of ERK/MAPK and PI3K/Akt pathway resulting in loss of neuroplasticity. Similarly, GSK-3β can also directly inhibit mitochondrial-mediated pathway involving BCL-2 accelerating neuronal death and synaptic loss. Theoretically, multiple cellular pathways associated decreased neuroplasticity involved in pathophysiology of BD can either be blocked of reversed by targeting GSK-3β. Multiple studies repeatedly showed that lithium and valproate inhibit GSK-3β activity, enhance β-catenin activities, and increase PI3K mediated Akt (Chalecka-Franaszek & Chuang, 1999; Chen et al., 1999; Stambolic, Ruel, & Woodgett, 1996). Thus GSK-3β inhibition is acknowledged to be a promising target to enhance neuroplasticity in the treatment of BD. Fig. 23.2 summarizes general concept of neuroplasticity disturbance in BD.

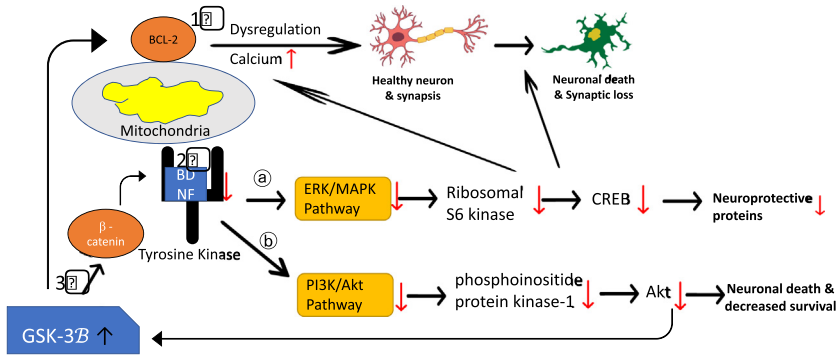

FIGURE 23.2 General concept of neuroplasticity disturbance in bipolar disorder (Dandekar et al., 2018; Soeiro-de-Souza et al., 2012). 1. Mitochondrial-mediated pathway: activation of proapoptotic BCL-2 family leads to excess calcium resulting in neuronal cell death and synaptic damage. 2. BDNF related pathway: decreased BDNF activities cause (a) decrement of ERK/MAPK pathway, which leads to lowered CREB activity; (b) decrement of PI3K/Akt signaling pathway, which leads to lowered Akt. Both (a) and (b) result in decreased neuroplasticity. 3. GSK-3β is closely associated with both mitochondrial-mediated pathway and BDNF related pathway. Thus, theoretically, by inhibiting GSK-3β majority of cellular pathway leading decreased neuroplasticity associated with BD can be blocked or prevented. *Akt*, protein kinase B; BDNF, brain-derived neurotrophic factor; *CREB*, cAMP response element-binding; *ERK*, extracellular regulated kinase; *MAPK*, mitogen-activated protein kinase; *PI3K*, phosphatidylinositol-3 kinase.

23.4 Neuroimaging studies

23.4.1 Structural magnetic resonance imaging

With the developmental of neuroimaging techniques, it has become possible to visualize plasticity changes per se and its negative impact of BD in human brain. Thus pathological changes in cellular level are now both visible and detectable in an anatomical level. The first wave of translating cellular level to anatomical level started with growing interest of underpinnings neurobiology of BD using structural magnetic resonance imaging (MRI) studies. As discussed earlier, cellular level studies showed that BD are associated with decrease in volume, density, number, and size of neuron and glial cells mainly in subgenual PFC, orbital cortex, dorso lateral PFC, amygdala, and basal ganglia (Cotter et al., 2001; Manji & Duman, 2001). In parallel, reduced gray matter volumes in areas of the orbital and medial PFC, ventral striatum and hippocampus, and enlargement of third ventricles were repeatedly observed in patients with BD (Selvaraj et al., 2012). Moreover, studies indicated that structural abnormalities are already present in first-episode schizophrenia or BD with significant overlap between the two. However, whole gray matter volume deficits and lateral ventricular enlargement were reported to be more prominent in first-episode schizophrenia whereas white matter volume reduction were more prominent in BD (De Peri et al., 2012). Likewise, evidences indicated that these structural brain abnormalities are already present in first-episode BD, but these do not overlap with those emerging from previous metaanalyses performed in patients with chronic BD (McIntosh et al., 2007). Taken these together, the loss of neuroplasticity observed in cellular or molecular level caused cortical and subcortical damage of brain in patients with BD. These findings also suggest that a distinct pattern of morphological changes occurs during the course of BD (Vita, De Peri, & Sacchetti, 2009). Studies showed that patients with longer illness duration have lower gray matter volume suggesting progression of BD could be associated with an abnormal cellular plasticity, especially of gray matter (Brambilla et al., 2001; Moorhead et al., 2007). An imaging study showed that adolescents with BD who were taking mood stabilizer had less volume loss (Chang et al., 2005). More importantly, patients who received long-term therapy with lithium showed an increase in gray matter volume over time, which suggested possibility of positive morphological and plastic alterations in the brain of treated BD patients (Moore et al., 2000; Sassi et al., 2002).

23.4.2 Diffusion tensor imaging

The structural MRI has advantages of assessing cortical volume loss or general cerebral atrophy. However, it has weakness in studying white matter because of its limited contrast detection in white matter tracts. In contrast, diffusion tensor imaging (DTI) is uniquely sensitive to white matter (WM)

microstructure analysis including axonal coherence, fiber density, and myelin integrity (O'Donnell & Westin, 2011). DTI applies two indices to investigate WM's physical integrity: the fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) (Alexander et al., 2007). It may be used to map and characterize the three-dimensional diffusion of water as a function of spatial location, so it has been used extensively to map white matter tractography in the brain (Alexander et al., 2007). Thus it is more sensitive to white matter microstructure analysis including axonal coherence, fiber density, and myelin integrity than conventional structural MRI (Le Bihan, 2003). Thus it provides more specific information on plasticity-related morphological tissue changes than conventional anatomical MRI (Voss & Schiff, 2009).

Multiple studies using region-of-interest based analysis showed that patients with BD exhibited lower FA compared to healthy controls, mainly in WM tracts of prefrontal areas, anterior cingulum, callosal areas, and limbic-striatal areas (Arnone et al., 2008; Beyer et al., 2005; Wang et al., 2008). Likewise, a metaanalysis of voxel-based analysis showed clusters of FA and mean diffusivity alterations in areas relevant for emotional processing (Marlinge, Bellivier, & Houenou, 2014). The voxel-based analysis-DTI studies repeatedly suggested existence of a disconnected framework within fronto-limbic areas as well as between fronto-limbic and temporal, parietal, and occipital lobes. For example, a recent metaanalysis of the voxel-based analysis-diffusion tensor imaging (VBA-DTI) studies showed significant clusters of decreased FA within right temporo-parietal WM, left cingulum, and left anterior cingulate in patients with BD (Nortje et al., 2013). Thus DTI studies have consistently shown an alteration in prefrontal−limbic anatomical connectivity (Bellani et al., 2016). Bellani et al. suggested that due to disconnection between prefrontal and limbic regions, the prefrontal cortices will be unable to downregulate limbic regions leading to emotional instability of BD.

WM alterations in BD have been regarded as a potential for drug discovery and development (Marlinge et al., 2014). A study showed that compared to controls and MDD patients, BD patients had significantly lower FA and increased ADC in the majority of the WM fiber bundles connecting structures of the anterior limbic network (Benedetti et al., 2011). The study further suggested that WM changes might be secondary to myelin sheaths damage, and lithium therapy might protect against such injury. Thus DTI studies could be reliable biomarkers which can be used for development and discover of new drugs for BD treatment.

23.4.3 Resting-state functional magnetic resonance imaging

Resting-state functional MRI (rs-fMRI), by measuring changes in resting-state blood oxygen level dependence, reflects cyclic modulation of gross

cortical excitability and neuronal synchronization signals (Zuo et al., 2010). Thus it provides a noninvasive and task-free approach that removes some performance-related confounds, so it could reflect measure of "baseline" brain activity, connectivity, and plasticity of brain (Guerra-Carrillo, Mackey, & Bunge, 2014). Among diverse large-scale brain networks, aberrance of default mode network (DMN) in BD is consistently reported. According to a recent systematic by Zovetti et al., a minimum of 23 studies investigated DMN connectivity in patients with BD (Zovetti et al., 2020). Most studies repeatedly confirmed that BD patients show aberrant functional connectivity either in frontal or posterior hubs of DMN. However, studies showed conflicting results in terms of type of aberrance (i.e., both hypo and hypoconnectivity) and involved anatomic regions (PFC, anterior and posterior cingulate cortex, and precuneus). The controversial results might be attributed to the fact that rs-fMRI were different depending on patient's manic, depressive, mixed, or euthymic phase (Anand et al., 2009; Chai et al., 2011; Chepenik et al., 2010).

Another meta-analysis investigated functional connectivity difference among health controls, BD patients, and major depressive patients (Gong et al., 2020). The study showed that patients with BD and MDD had common increment of amplitude of low-frequency fluctuation (ALFF) in the bilateral insula and right medial prefrontal cortex (mPFC) and decrement of ALFF in the left cerebellum posterior lobe. The study further showed that patients with BD had a different regional intrinsic activity from that of patients with MDD. The neuroplastic change illustrated by fMRI were also known to be associated with symptom severity differently in BD and MDD. In patients with MDD, metaregression showed that higher depressive symptoms measured via Hamilton Depression Symptom Scale (HAM-D) was correlated with greater increases in ALFF in the right anterior cingulate cortex (ACC). However, in patients with BD, higher HAM-D was associated with greater decreases in ALFF in the right posterior cingulate cortex (PCC). A more recent study found that BD patients presented different connectivity pattern depending on its disease state (Wang et al., 2020). In acutely ill state, decreased connectivity within the affective network and DMN were noted, which disappeared in the remitted state. Authors further suggested that rs-fMRI could become an important clinically relevant biomarker in guiding treatment strategies for BD. However, there remain issues such as reproducibility of results and lack of data demonstrating longitudinal changes of fMRI findings in BD before it can widely be used as a surrogate biomarker.

23.4.4 Neuroinflammation

Inflammation, by providing protective response to harmful stimuli, such as pathogens, damaged cells, or irritants, play an important role in plasticity (Medzhitov, 2010). Increased neuroinflammation corresponds to activation

of microglia, the resident macrophages of the brain, which is known to be associated with abnormalities of cerebral plasticity such as lowered hippocampal volume (Beumer et al., 2012). Mounting evidences showed strong association between inflammation and neural plasticity, and recent researches further suggested that neuroinflammation might serve as marker reflecting neuroplasticity (Golia et al., 2019; Singhal & Baune, 2017).

With recent advance imaging technique, microglia activation reflecting neuroinflammation can now be visualized in vivo with the radioactive contrast [11C]-(R)-PK11195 by means of positron emission tomography (PET). In a study comprising 14 patients with BD and 11 healthy controls, patients with BD showed a significantly increased [11C]-(R)-PK11195 binding potential, which is indicative of neuroinflammation, in the right hippocampus than HC (Haarman et al., 2014). A more recent study conducted by the same research group compared hippocampal volume and metabolites in bipolar I disorder (BD-I) patients with HCs using MRI and spectroscopy (Haarman et al., 2016). The study furthered early finding by showing that *N*-acetylaspartate (NAA) + *N*-acetyl-aspartyl-glutamate (NAAG) concentration were decreased in the left hippocampus of BD-I patients which suggested that there was a decreased neuronal integrity or lowered plasticity in this region.

23.5 Drugs development targeting GSK-3β

As stated earlier in the chapter, by targeting GSK-3β, multiple detrimental cascades related to neuroplasticity can be blocked simultaneously (Fig. 23.2). Thus majority of molecules targeting neuroplasticity act via GSK-3β inhibition. Pharmacological inhibitors of GSK-3β could be classified into three following categories: (1) competition with either adenosine triphosphate (ATP) or metal-binding sites that are involved directly in the catalytic process (ATP-competitive inhibitors); (2) primed phosphorylated Ser 9 binding area necessary for binding of substrate (substrate competitive inhibitors); (3) targeting kinase selectivity (non-ATP-competitive inhibitors) (Dandekar et al., 2018).

An initial study showed that AR-A014418, an ATP-competitive inhibitors of GSK-3β inhibitors, crossed blood−brain barrier and reduced immobility time in rats exposed to the forced swim test, which is a well-established model for antidepressant efficacy (Gould et al., 2004). The study further showed that AR-A014418 decreased amphetamine-induced activity and suggested that it could be a potential molecule to treat BD, especially for bipolar depression. A more recent study showed that AR-A014418 has an antimanic effect by illustrating that it can reverse behavioral and oxidative stress related to manic symptoms induced ouabain (OUA) (Dal-Pont et al., 2019). OUA is known to mimic manic-like symptoms, such as hyperactivity, risk-taking behavior, and stereotypic behaviors via inhibition of Na + K + ATPase activity (El-Mallakh et al., 2003). L803-mts is another

selective peptide inhibitor GSK-3β. A study showed that mouse injected intracerebroventricularly with L803-mts showed less immobility time in forced swim test (Kaidanovich-Beilin et al., 2004). The study further showed that L803-mts significantly inhibited purified GSK-3β, and expression levels of beta-catenin was increased in the hippocampus of L803-mts-treated mouse by 50% compared to control peptide treated mouse. The upregulation of beta-catenin, as stated earlier, is known to be associated with inactivation of GSK-3β (Sakanaka, Weiss, & Williams, 1998).

Most of the GSK-3β inhibitors developed so far are ATP-competitive inhibitors. However, ATP binding site is highly conserved among numerous other protein kinases. Thus ATP-competitive inhibitor have a serious limitation regarding its low specificity resulting in frequent off-target effects (Eldar-Finkelman et al., 2010). In contrast, substrate competitive inhibitors are expected to be more specific, but its weak binding interaction with the enzyme is its major limitation. Due to this advantage substrate-competitive inhibitors have often been overlooked. In the other perspective, studies showed that the GSK-3β over-expression does not exceed twofold to threefold over normal levels even in a pathological state. Therefore moderate-to-weak inhibition of GSK-3β activity would be sufficient to provide good selectivity with desired treatment effect (Dandekar et al., 2018). Palomo et al. reported substituted 5-imino-1,2,4-thiadiazoles as the first small molecules able to inhibit GSK-3β as a substrate competitive inhibitor (Palomo et al., 2012). The study showed that it can decrease inflammatory activation and selectively differentiate neural stem cells resulting in protection against neuronal cell death and promote endogenous neurogenesis by blocking the GSK-3β substrate site. It is also known to cross blood−brain barrier penetration and bind to human serum albumin showing good drug-like properties (Perez et al., 2012).

In line with substrate competitive inhibitors, achieving kinase selectivity is one of the major obstacles in drug discovery and design of non-ATP-competitive inhibitors (Eglen & Reisine, 2009). The major advantage of non-ATP-competitive inhibitors is that only pathologic GSK-3β can be inhibited without causing effect to GSK-3α. By doing so, it may be possible to achieve high potency with reduced toxicity. However, discovering such molecules is very difficult because the isoenzymes GSK-3α and GSK-3β share more than 98% homology. Tideglusib (NP-12, P031112) is a potent and irreversible non-ATP-competitive inhibitor for GSK-3β (Dominguez et al., 2012). Animal studies showed that it has neuroprotective, antiinflammatory, and neurogenesis-inducing effects (Wang et al., 2016). More importantly, tideglusib is shown to inhibit tau phosphorylation, amyloid deposition, and neuron loss. Thus most studies were done in Alzheimer's disease and other neurodegenerative disorder such as Progressive Supranuclear Palsy, and they all have entered clinical phase (i.e., Phase II for Alzheimer's disease) (del Ser et al., 2013). Thiadiazolidinone-8 (TDZD-8), another non-

ATP-competitive inhibitor, is an effective thiadiazolidinone derivate that is able to suppress the expression of inflammatory cytokines; it also presents tissue protective actions by GSK-3β inhibition, promoting thus an antiinflammatory effect. Earlier studies showed that it can decrease immobility time in a tail suspension test (Belmaker, Agam, & Bersudsky, 2008) but more recent studies focused on its pro-cognitive and antiinflammatory effect for diverse neurodegenerative disorder including Alzheimer's disease. Table 23.1 provides summary of investigational drug with GSK-3β inhibition effect.

23.6 Summary

A plethora of research indicated that disturbance of plasticity, or more specifically neuroplasticity, plays an important role in the pathophysiology of BD. The evidence is repeatedly found in cellular studies which became visible and detectable via various neuroimaging studies. The development of neuroimaging studies enabled us to assess diverse changes of neuroplasticity with greater time and space resolution. Investigating volumetric decrement using structural MRI can reflect neuronal damage and cellular death, white matter tract damage with DTI can represent myelination change, functional connectivity aberration with rs-fMRI can show synaptic dysfunction, and PK11195 PET study can mirror neuroinflammatory change of BD. Thus diverse biomarkers related with neuroplasticity can serve as a key target for the future treatment of BD.

In terms of drug development, studies consistently reported that classic mood stabilizers including lithium and valproate exert their effect by inhibiting GSK-3β. Moreover, multiple cellular pathways associated decreased neuroplasticity including mitochondrial-mediated pathway, ERK/MAPK pathway, and PI3K/Akt signaling pathway could be targeted simultaneously by inhibiting GSK-3β. Thus most investigational molecules developed to date work as GSK-3β inhibitors. Despite promising findings, none of GSK-3β inhibitors or drugs enhancing neuroplasticity reached the market. Several promising GSK-3β inhibitors failed in the diverse developmental phase due to their poor selectivity and weak BBB permeability. Future studies should focus on increasing the selectivity and BBB permeability to increase its potential as a viable target for BD.

TABLE 23.1 Investigational drug for bipolar disorder (BD) with GSK-3β inhibition effect.

Molecule	Mode of action	Study phase	Findings	Target	Study
AR-A014418	ATP-competitive inhibitors	Preclinical	Reduced immobility time in rats exposed to forced swim test	BD-depression	Gould et al. (2004)
		Preclinical	Reverse OUA-induced behavior disturbance	BD-manic	Dal-Pont et al. (2019)
L803-mts	ATP-competitive inhibitors	Preclinical	Reduced immobility time in forced swim test. Upregulation of beta-catenin	BD-depression	Kaidanovich-Beilin et al. (2004)
5-Imino-1,2,4-thiadiazoles	Substrate competitive inhibitors	Preclinical	Decrease neuronal cell death.Increase neurogenesis	Neuroinflammation	Palomo et al. (2012)
Tideglusib (NP-12, NP031112)	Non-ATP competitive inhibitors	Clinical	Neuroprotective,antiinflammatory,neurogenesis. Inhibit tau phosphorylation, amyloid deposition, neuron loss	Alzheimer's disease	Wang et al. (2016)
TDZD-8	Non-ATP competitive inhibitors	Preclinical	Antiinflammatory effect	BD-depression	Belmaker et al. (2008)

OUA, Ouabain; *TDZD-8*, Thiadiazolidinone-8.

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