# Synaptic Plasticity in the Pathophysiology and Treatment of Bipolar Disorder

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**Abstract** Emerging evidence suggests that synaptic plasticity is intimately involved in the pathophysiology and treatment of bipolar disorder (BPD). Under certain conditions, over-strengthened and/or weakened synapses at different circuits in the brain could disturb brain functions in parallel, causing manic-like or depressive-like behaviors in animal models. In this chapter, we summarize the

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regulation of synaptic plasticity by medications, psychological conditions, hormones, and neurotrophic factors, and their correlation with mood-associated animal behaviors. We conclude that increased serotonin, norepinephrine, dopamine, brain-derived neurotrophic factor (BDNF), acute corticosterone, and antidepressant treatments lead to enhanced synaptic strength in the hippocampus and also correlate with antidepressant-like behaviors. In contrast, inhibiting monoaminergic signaling, long-term stress, and pathophysiological concentrations of cytokines weakens glutamatergic synaptic strength in the hippocampus and is associated with depressive-like symptoms.

**Keywords** BDNF · Bipolar disorder · Cytokine · Mood stabilizer · Stress · Synaptic plasticity

## 1 Introduction

There is an urgent need to identify the functional mechanisms associated with bipolar disorder (BPD) in order to develop novel and effective therapeutics. This has led investigators to explore synaptic function, and recent studies from our and other laboratories have consistently suggested that synaptic plasticity of the glutamatergic system may be the convergent mechanism for the treatment of BPD (Carlezon and Nestler 2002; Du et al. 2004a, 2008; Manji et al. 2003; Zarate et al. 2006).

Indeed, Berman et al. (2000) reported the first placebo-controlled, double-blind trial to assess the effects of a single dose of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine in seven patients with major depressive disorder (MDD). Zarate et al. (2006) subsequently described that a single intravenous dose of ketamine showed robust, rapid, and long-lasting antidepressant effects in patients with treatment-resistant MDD; the same investigators are currently assessing the therapeutic effects of ketamine in patients with bipolar depression. These studies bring new hope for the development of fast-acting medications for BPD.

In addition, accumulating evidence from preclinical studies suggests that α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor (AMPAR) antagonists attenuate several "manic-like" behaviors, mimicking BPD, produced by amphetamine administration. Studies demonstrating that AMPAR antagonists reduce amphetamine/cocaine-induced hyperactivity and hedonic behavior (Dalia et al. 1996; Layer et al. 1993; Li et al. 1997b; Mead and Stephens 1999; Tzschentke and Schmidt 1997) provide compelling behavioral support for the notion that AMPARs play key roles in regulating affective behavior. A recent study from our laboratory found that the structurally dissimilar antimanic agents lithium and valproate both reduced synaptic expression of AMPAR subunits GluR1 and GluR2 at synapses in vivo and in vitro in the hippocampus (Du et al. 2003, 2004a, 2008). In contrast, the antidepressant agents imipramine, lamotrigine, and

riluzole enhanced surface AMPAR expression and phosphorylation of GluR1S845 in the hippocampus in vivo (Du et al. 2007). These data suggest that glutamatergic synaptic plasticity may be the convergence point for the treatment of BPD.

More recently, the traditional monoamine focus for mood disorders has been extended to encompass their downstream signaling targets for regulation of synaptic plasticity. In this chapter, we will summarize recent findings regarding the modulation of synaptic plasticity by pharmacological, environmental, hormonal, and biological factors, and their correlative effects on mood-associated behaviors. We will specifically focus on the regulation of synaptic plasticity in the hippocampal and prefrontal cortical brain regions because these two regions are closely related to mood disorders and the data are well established.

## 2 Synaptic Plasticity in Psychoneurobiology

Broadly, synaptic plasticity is the ability of the synapses to respond and adapt to neuronal activity and environmental stimuli in order to remodel neurotransmitter release, synaptic strength, and synaptic stability (Citri and Malenka 2008; Malenka 2003a). More than 100 billion neurons function in the adult human brain, and each neuron interconnects with thousands of synapses. A single behavioral action may therefore be translated into the activation of a large number of synapses in the relevant neuronal circuits. It is believed that behavioral experiences or medications can modify synapses, thereby strengthening some neuronal pathways within a circuit, and weakening others (Kessels and Malinow 2009; Shepherd and Huganir 2007). Therefore, the major goals of modern psychoneurobiology and psychopharmacology must encompass the identification of brain synaptic plasticity and the circuits modified by experience or medicines that lead to changes in mood-associated behaviors.

Synaptic plasticity has been extensively studied via long-term potentiation (LTP), which is typically induced by high-frequency stimulation (HFS) of excitatory input leading to rapid elevation of calcium in postsynaptic dendritic spines (Blundon and Zakharenko 2008; Bramham 2008). This essential calcium influx at most excitatory synapses is provided by activating AMPARs and, subsequently, NMDA-type glutamate receptors; this occurs in combination with the contributions from voltage-gated calcium channels and mobilization of calcium from intracellular stores. LTP can last for weeks and months and can be evoked by both HFS and chemicals. It is well established that maintenance of LTP involves at least two phases, including early LTP and late LTP. Early LTP, which lasts about 1–2 h, requires phosphorylation of existing proteins (i.e., GluR1S845 or GluR1S831) and protein trafficking at synapses, but not new protein synthesis. Late LTP, like long-term memory, depends on protein synthesis (Blundon and Zakharenko 2008; Bramham 2008).

Although the mechanisms of LTP and long-term depression (LTD) have not been completely elucidated, it is widely accepted that AMPAR trafficking is key to these phenomena, especially during early phase LTP (Kessels and Malinow 2009;

Shepherd and Huganir 2007). Trafficking of AMPA-type glutamate receptors serves as a prevalent mechanism underlying activity-induced changes in synaptic transmission. AMPARs comprise four homologous subunits (GluR1–4), which assemble into various heteromeric tetramers. In the adult hippocampus, most AMPARs contain GluR1 or GluR3 subunits in combination with GluR2, which confers calcium impermeability. However, phosphorylation of the GluR1 receptors by protein kinase A (PKA), protein kinase C (PKC), and calcium/calmodulin-dependent protein kinases (CAMKII) is highly regulated, and several signal transduction cascades can produce short- and long-term changes in the expression of AMPAR subunits at the synaptic surface (Kessels and Malinow 2009; Shepherd and Huganir 2007). In particular, phosphorylation of GluR1 at serine 845 leads to the insertion of AMPARs into the neuronal membrane and the wide opening of AMPAR ion channels, thus serving as a marker for synaptic strength in various psychological conditions (Kessels and Malinow 2009; Shepherd and Huganir 2007).

LTP is associated with both rapid (in minutes) and more delayed (in hours or days) changes in gene expression (Davis and Laroche 1998). After HFS, several constitutively expressed transcription factors, including cyclic-AMP/calcium responsive-element binding protein (CREB) and Elk-1, are activated, leading to enhanced transcription of a functionally diverse group of immediate early genes. CREB is also a key factor and is an associated gene for depression. The protein synthesis-dependent consolidation plays an essential role in various forms of long-term synaptic plasticity and animal behaviors (Kandel et al. 2001). The long-term changes usually lead to the strengthening of the synapses structurally or the formation of the new synapses (Bredt and Nicoll 2003; Hu et al. 2008; Massaro et al. 2009). In addition to the association between synaptic plasticity and learning and memory, a growing body of data suggests that synaptic plasticity is the key regulator for psychiatric disorders and drug addiction. Indeed, synaptic plasticity is a fundamental mechanism for neuronal communication.

## 3 Synaptic Plasticity Is a Common Target of the Mood Stabilizers Lithium and Valproate

Lithium and valproate are structurally dissimilar mood stabilizers which are used to treat mania for decades. Accumulating data demonstrate that mood stabilizers regulate several intracellular signaling pathways that regulate synaptic plasticity, including PKC, PKA, mitogen-activated protein (MAP) kinase, glycogen synthase kinase 3ß (GSK-3ß), and intracellular calcium (Lee 2006; Manji et al. 2003). In this context, it is notable that a growing body of data indicates that synaptic plasticity, and particularly AMPAR trafficking, might be involved in the pathophysiology and treatment of mood disorders.

Recent studies found that the mood stabilizers lithium and valproate appear to attenuate glutamatergic function via multiple mechanisms. Repeated administration of lithium appears to promote the uptake of glutamate from the synapse

(Dixon and Hokin 1998), alter the function of glutamate receptors (Du et al. 2004b, 2008; Gould et al. 2008; Nonaka et al. 1998), and reduce the function of intracellular signaling cascades (Manji et al. 1999). Chronic treatment with lithium also leads to a decreased AMPA/NMDA ratio, which is mainly caused by reduction of AMPARs at the synapses (Du et al. 2008). In addition, both lithium and valproate reduced AMPAR GluR1 and GluR2 levels at synapses of hippocampal neurons. This reduction in synaptic GluR1/2 by lithium and valproate was due to attenuated phosphorylation of GluR1 at a specific PKA site (residue 845 of GluR1), which is crucial for AMPAR insertion (Du et al. 2004a, 2008). Notably, both lithium and valproate inhibit GSK-3, and lithium, valproate, and other GSK-3 inhibitors demonstrate both antimanic and antidepressant efficacy in animal models of mood-associated behaviors (Gould et al. 2004; Kapus et al. 2008). Lithium's antidepressant effects were inhibited by the AMPAR antagonist GYKI52446 (Gould et al. 2008). Rats receiving hippocampal infusions of AMPA-specific inhibitors exhibited significant reductions in manic behaviors as assessed through the amphetamine-induced locomotion and conditioned place preference (CPP) paradigms, both of which are well-validated animal models of mania (Du et al. 2008). In contrast, the tricyclic antidepressant (TCA) imipramine, which can provoke mania in patients, increases synaptic expression of GluR1 in the hippocampus in vivo. Thus, it appears that mood stabilizers may exert their effects by regulating AMPA synaptic strength in the hippocampus.

## 4 Modulation of Synaptic Plasticity by the Monoaminergic Systems: Serotonin, Norepinephrine, and Dopamine

Modulatory transmitters such as norepinephrine, serotonin, dopamine, and acetylcholine are all involved in regulating, inducing, or maintaining LTP (Bramham et al. 1997; Bramham and Srebro 1989; Harley 2004; Kulla and Manahan-Vaughan 2002; Stanton and Sarvey 1985a, b; Straube et al. 2003; Swanson-Park et al. 1999). These extrinsic inputs typically have diffuse, global patterns of innervation to the corticolimbic system. Neuronal firing activity in these systems is tied to mood-associated behaviors. Furthermore, these classic modulatory transmitters can affect gene expression by affecting PKA and CREB activity. Recently, a theory of altered neuroplasticity as a neurophysiologic condition for mood disorders was proposed (Bramham 2007; Pittenger and Duman 2008). Below, we discuss the regulation of synaptic plasticity by monoaminergic systems.

### *4.1 Serotonin*

Antidepressants modulate synaptic plasticity, particularly LTP (Kasper and McEwen 2008; Pittenger and Duman 2008); however, the effect of antidepressants

on hippocampal synaptic plasticity remains unclear (Holderbach et al. 2007; Massicotte et al. 1993; Matsumoto et al. 2005; Stewart and Reid 2000; Wang et al. 2008). Chronic application of fluvoxamine during the stress protocol prevented the facilitation of LTD induced by exposure to chronic mild stress and increased LTP induction (Holderbach et al. 2007). In addition, imipramine, fluoxetine, and other antidepressants increase the phosphorylation of GluR1 at S845 and S831, both of which serve as markers for the occurrence of LTP (Du et al. 2007; Svenningsson et al. 2007; Szabo et al. 2009).

Accumulating data have shown that serotonin affects LTP and LTD in slice preparations. The effect differs by receptor subtype, timing, and interaction with other factors. Serotonin and serotonergic subreceptors can either facilitate or block LTP as well as LTD, depending on subreceptor specificity, neuronal type, location of plasticity induction, and frequency of application (Abe et al. 2009; Edagawa et al. 1999, 2000; Inaba et al. 2009; Machacek et al. 2001; Normann and Clark 2005; Ryan et al. 2008; Sanberg et al. 2006). Serotonin is also a potential candidate for modulating synaptic plasticity with novel stimuli (Kemp and Manahan-Vaughan 2004), and it is thought to play an important role in mood and anxiety disorders. Previous studies reported that serotonin releasers facilitate the response of dentate granule cells to perforant path stimulation (Winson 1980), an effect thought to be mediated by the 5-HT1a receptor (Levkovitz and Segal 1997). Recent studies also found that stimulation of basolateral amygdaloid serotonin 5HT2C promotes the induction of LTP in the dentate gyrus of the rat hippocampus (Abe et al. 2009). In rodents, the 5HT1A receptor may also mediate perforant path dentate LTP induced by novel environments (Sanberg et al. 2006). Although the effect of serotonin on LTP depends on receptor subtype and neuronal type, most evidence suggests that enhancing serotonergic signaling facilitates the formation of LTP in the perforant path.

## *4.2 Norepinephrine*

The stress hormone norepinephrine plays a central role in regulating emotions via brain β-adrenergic receptors (Cahill and Perlman 1994; Ferry and McGaugh 2000). During stress, norepinephrine is released by neurons originating from the locus coeruleus and lateral brain stem tegmentum to many brain regions, including the hippocampus and the amygdala, both of which are key to mood-associated behaviors (Carrasco and Van de Kar 2003). Norepinephrine and β-adrenergic stimulation show profound effects on facilitation of LTP induction in the hippocampus CA1 region (Gelinas et al. 2008; Gelinas and Nguyen 2005; Katsuki et al. 1997; Sarvey et al. 1989). Recent studies also show that norepinephrine signaling induces phosphorylation of the Ser845 and Ser831 sites of GluR1 both in vitro and in vivo. Norepinephrine and phosphomutant mice with knockin mutations on the GluR1 phosphorylation sites have similar defects in norepinephrine-facilitated LTP and norepinephrine-enhanced contextual memory tasks (Hu et al. 2007).

### *4.3 Dopamine*

Previous studies strongly suggest that dopamine promotes the induction of LTP at CA1 synapses in the rat hippocampus after exposure to a novel spatial environment (Li et al. 2003). Furthermore, dopamine release in the hippocampus enhances LTP and learning, suggesting a link between synaptic plasticity and rewarding circuitry (Li et al. 2003; Lisman and Grace 2005). Recent studies revealed that the critical factor regulating LTP and LTD induction in the hippocampus is the level of tonic background of dopamine (Kolomiets et al. 2009; Matsuda et al. 2006). LTP induction in the hippocampus–prefrontal cortex (PFC) pathway is disrupted by PFC dopamine fiber de-enervation with 6-hydroxydopamine and pretreatment with dopamine D1 receptor inhibitor in vivo (Gurden et al. 2000). D1 receptor activation facilitates calcium influx and activates signaling cascades, including PKA, which subsequently phosphorylates AMPAR GluR1 at S845 and promotes the insertion of AMPARs into the synapses (Greengard et al. 1999; Sun et al. 2008). Taken together, the evidence suggests that dopamine signaling enhances and facilitates the formation of LTP in the hippocampus and PFC.

## 5 Brain-Derived Neurotrophic Factor Is a Key Modulator of Synaptic Plasticity

Brain-derived neurotrophic factor (BDNF), an important neurotrophin highly expressed in the brain, is best known for its role in regulating synaptic plasticity and its neuroprotective effects against various hazardous stimuli (Kuipers and Bramham 2006; Popoli et al. 2002). Several lines of evidence also suggest that BDNF is involved in depression (Kuipers and Bramham 2006; Popoli et al. 2002). For instance, the expression of BDNF is decreased in depressed patients, and antidepressants up-regulate its expression (Duman 2004; Hashimoto et al. 2004). Furthermore, infusion of BDNF into the rodent brain resulted in antidepressant effects in animal models of depression (Shirayama et al. 2002). It is also interesting to note that human genetic studies found that individuals with BPD who have the Val/Met, rather than the Val/Val form of BDNF, had a more favorable response to lithium, suggesting that the prophylactic effects of lithium could be increased in patients with lower BDNF activity (Frey et al. 2006; Yu et al. 2009). In support of this theory, the mood stabilizers lithium and valproate were found to increase BDNF expression in the rat brain, suggesting that BDNF's neurotrophic effects may contribute to its therapeutic efficacy (Frey et al. 2006; Yu et al. 2009).

BDNF also contributes to a range of adaptive neuronal responses at the synapses including LTP, LTD, certain forms of short-term synaptic plasticity, and homeostatic regulation of intrinsic neuronal excitability. The unique role that BDNF plays as a major regulator of synaptic transmission and plasticity within the neurotrophin family fits with the widespread distribution of BDNF and the

colocalization of BDNF and its receptor, TrkB, at glutamatergic synapses (Lu et al. 2008; Lynch et al. 2007). The molecular mechanisms and function of BDNF in modulating LTP have been well established in the hippocampus. BDNF activates distinct mechanisms to regulate the induction, early maintenance, and late maintenance phases of LTP (Lu et al. 2008; Lynch et al. 2007). BDNF modulates LTP by inhibiting synaptic fatigue, which is a reduction in excitatory postsynaptic potential (EPSP) amplitude observed in response to theta burst stimuli (Lu et al. 2008; Lynch et al. 2007). Inhibition of BDNF signaling by TrkB-Fc to sequester extracellular TrkB ligands enhanced synaptic fatigue and impaired both the induction and early maintenance of LTP at CA3–CA1 synapses in adult rat hippocampal slices (Figurov et al. 1996). In an analysis of BDNF knockout mice, two groups independently reported impaired early LTP in mice homozygous or heterozygous for BDNF (Korte et al. 1995; Patterson et al. 1996). These studies suggest that BDNF is a key modulator of synaptic plasticity in vivo.

## 6 Neural and Synaptic Plasticity During Chronic Stress

Corticosteroids, such as prednisone and dexamethasone, are commonly prescribed medications that suppress the immune system and decrease inflammation, but are associated with psychiatric and cognitive side effects (Daban et al. 2005; Marshall and Garakani 2002). Hypomania and mania are the most common mood changes during acute corticosteroid therapy. However, depression appears to be more common than mania during long-term treatment with corticosteroids (Laakmann 1988; Sonino and Fava 2001). Similar results were reported in patients with Cushing's syndrome (Laakmann 1988; Sonino and Fava 2001). A decline in declarative and working memory has also been reported during corticosteroid therapy (Daban et al. 2005; Laakmann 1988; Sonino and Fava 2001). Mood and cognitive symptoms are dose-dependent and frequently occur during the first few weeks of therapy. Controlled trials suggest that lithium can prevent mood symptoms associated with corticosteroids (Daban et al. 2005).

Glucocorticoids enter the hippocampus and exert their function through mineralocorticoid and glucocorticoid receptors. In vivo, behavioral stressors cause long-lasting potentiation of NMDA receptor (NMDAR)- and AMPAR-mediated synaptic currents via glucocorticoid receptors selectively in PFC pyramidal neurons. This effect is accompanied by increased surface expression of NMDAR and AMPAR subunits in acutely stressed animals (Maggio and Segal 2009; Setiawan et al. 2007; Venkova et al. 2009). Furthermore, behavioral tests indicate that working memory, a key function that relies on recurrent excitation within networks of PFC neurons, is enhanced by acute stress via a glucocorticoid receptor-dependent mechanism (Yuen et al. 2009).

The stress hormone corticosterone exerts marked effects on learning and memory. It can both facilitate and impair these functions, suggesting that short-term versus long-term treatment may exert opposite effects (Sandi and Pinelo-Nava 2007). Interestingly, corticosteroid hormones profoundly affect AMPAR function, synaptic transmission, and plasticity via genomic and nongenomic pathways. These rapid, nongenomic effects of corticosterone are mediated via high-affinity mineralocorticoid receptors that act to enhance AMPAR miniature excitatory postsynaptic current (mEPSC) frequency and facilitate synaptic potentiation (Maggio and Segal 2009; Setiawan et al. 2007; Venkova et al. 2009). In one model, corticosterone increases associated with a stress paradigm significantly increased LTP in the hippocampal CA1 regions (Alzoubi et al. 2005; Yang et al. 2004). These effects were believed to occur through nongenomic mechanisms. Long-lasting effects were mediated via glucocorticoid receptors that enhance AMPAR-mediated mEPSC amplitude, impair NMDAR-mediated LTP, and facilitate LTD (Alzoubi et al. 2005; Yang et al. 2004). Recent studies also found that corticosteroids regulate AMPAR insertion on the neuronal membrane, providing a molecular mechanism for LTP and LTD (Campioni et al. 2009; Conboy and Sandi 2010; Martin et al. 2009). Therefore, acute, short-term corticosterone enhanced the formation of LTP; however, long-term treatment inhibited the formation of LTP and facilitated formation of LTD. Notably, acute increases in stress hormones lead to mania, and long-term stress leads to depression (Conboy and Sandi 2010; Pittenger and Duman 2008; Popoli et al. 2002).

## 7 Proinflammatory Cytokines in Regulating Synaptic Plasticity: Potential Implications for Mood Disorders

The interactions between the immune and central nervous system (CNS) in various pathological conditions such as brain trauma, mood disorders, and neurodegenerative diseases have been well studied. Considerable evidence suggests that cytokines also play an important physiological role in normal CNS function at both the cellular and molecular level. The relative abundance of proinflammatory cytokines in specific brain areas involved in regulating learning and memory, such as the hippocampus, suggests their potential role in synaptic plasticity. (Carlezon and Nestler 2002; Du et al. 2004a, 2007, 2008; Kendell et al. 2005; Malenka 2003b; Sun et al. 2005; Wolf et al. 2004).

### *7.1 Regulation of Synaptic Plasticity by Tumor Necrosis Factor-α*

Altered levels of tumor necrosis factor (TNF)-α have been found in several neuropathological states associated with learning and memory deficits, such as depression

and Alzheimer's disease, thus raising the intriguing possibility that TNF-α may play a putative role in regulating neuroplasticity. Indeed, pathophysiological levels of TNF-α have been shown to inhibit LTP in the CA1 region, as well as the dentate gyrus of the rat hippocampus (Butler et al. 2004; Cunningham et al. 1996; Tancredi et al. 1992). More specifically, TNF-α has been shown to inhibit LTP in a biphasic manner; inhibition of early phase LTP by TNF-α depends on a p38MAPK process, whereas late phase LTP inhibition is p38MAPK-independent (Butler et al. 2004). Further studies also found that TNF-α inhibition of LTP is mediated via TNFR-1 and mGluR5 receptor-activated pathways (Cumiskey et al. 2007).

Although most studies suggest that TNF-α has deleterious effects on synaptic plasticity, recent evidence shows that physiologically low levels of TNF-α may play an important role in neurodevelopment, as well as in regulating homeostatic synaptic plasticity, namely "synaptic scaling" (Golan et al. 2004; Stellwagen and Malenka 2006). TNF-α released from glial cells in response to decreased neuronal activity potentiates membrane trafficking of synaptic AMPARs, and thus synaptic strength, and is therefore critical for homeostatic adjustment of neuronal excitability. Conversely, removal of TNF-α from brain slices results in weakened synapses (Beattie et al. 2002), suggesting that glially released TNF-α plays an important role both in adjusting synaptic strength and in maintaining it at appropriate levels. This TNF-α-induced AMPAR membrane trafficking depends on activation of TNF-R1 receptors and is selective for calcium-permeable AMPAR subunits.

## *7.2 Regulation of Synaptic Plasticity by IL-1*

In addition to its well-known role in immunoregulating inflammatory processes, emerging evidence suggests that IL-1 may modulate synaptic plasticity and behavioral systems. Early studies have suggested that IL-1 inhibits LTP induction in hippocampus (Cunningham et al. 1996; Murray and Lynch 1998). In accordance with this finding, several cognitive-behavioral studies in animals have repeatedly shown that high pathophysiological levels of IL-1 have a detrimental effect on hippocampal-dependent memory and learning processes (Barrientos et al. 2002; Bellinger et al. 1993; Curran and O'Connor 2001; Gibertini et al. 1995; Goshen et al. 2008; Oitzl et al. 1993; Pugh et al. 1999), while stress-induced inhibition of hippocampus-dependent conditioning can be reversed by IL-1ra, an IL-1 receptor antagonist (Maier and Watkins 1995; Pugh et al. 1999, 2000). Recent studies observed that increased IL-1 levels disrupted an LTP-associated spinal learning paradigm (Avital et al. 2003). Although most findings to date indicate that IL-1 has deleterious effects on synaptic function and memory, recent evidence suggests that, like TNF-α, it may also be required for the physiological regulation of hippocampal plasticity. IL-1 also inhibited the formation of LTP in the hippocampus, and

phosphorylation as well as trafficking of AMPARs (Lai et al. 2006; Ross et al. 2003).

### *7.3 Regulation of Synaptic Plasticity by IL-6*

IL-6 inhibits LTP induction without affecting previously established LTP via the MAP kinase/ERK pathway (MAPK-ERK) (Li et al. 1997a; Tancredi et al. 2000). In addition, IL-6 is up-regulated after LTP induction, and neutralizing IL-6 after HFS strengthens LTP maintenance (Balschun et al. 2004; Jankowsky et al. 2000). Taken together, these findings suggest that IL-6 appears to play a role in synaptic plasticity and may be required for fine-tuning the consolidation of long-term synaptic plasticity and hippocampal-dependent learning (Balschun et al. 2004; McAfoose and Baune 2009).

## 8 Brain Imaging Studies of Patients with BPD Demonstrate Changes in Neural Plasticity in the Brain Circuits Associated with Mood Disorders

BPD is associated with considerable structural impairment, potentially due to changes in cellular resilience and neuroprotection. Reduced gray matter volume in the ventral/orbitalmedial PFC and amygdala has been described (Brambilla et al. 2005; Konarski et al. 2008). One recent study noted volumetric reductions in discrete fronto-limbic cortex areas in individuals with BPD compared to healthy controls (Savitz and Drevets 2009). Several independent researchers have noted reduced subgenual PFC in individuals with BPD; this decrease is also associated with therapeutic response (Drevets et al. 1997; Hirayasu et al. 1999; Sharma et al. 2003). Similarly, volumetric and density abnormalities have been described in other areas of the PFC including the ventral and the ventromedial PFC, the orbitofrontal cortex, the posterior cingulate cortex, and the frontal gyri (Adler et al. 2004; Lyoo et al. 2004; Nugent et al. 2006).

Increased white matter hyperintensities (WMH) is a consistently replicable neuroimaging finding in individuals with BPD compared to healthy controls (Altshuler et al. 1995). This finding has been linked to a higher prevalence of cognitive dysfunction and greater severity of symptoms in mood disorders (Salvadore et al. 2008). Notably, evidence suggests that WMH represent damage to the structure of brain tissue and may disrupt neuronal connectivity (Sheline 2000). In addition, multiple episodes of BPD are associated with greater ventricular volumes (Strakowski et al. 2002), but not with gray matter loss in periventricular structures in BPD (Brambilla et al. 2001; Strakowski et al. 2002). Magnetic resonance spectroscopy (MRS) studies conducted over the last decade have also

reported widespread abnormalities in gamma aminobutyric acid (GABA), Glx (a combined measure of glutamate and glutamine), and glutamate levels in patients with BPD. MRS studies have also noted abnormalities in GABA and glutamate levels in mood disorders; these may be closely related to synaptic activity and reuptake of neurotransmitters in the interplay between glia and neurons in the PFC (Bhagwagar et al. 2007; Dager et al. 2004; Frey et al. 2007).

## 9 Synaptic Plasticity Models for Mood Disorders and Future Directions

Ample evidence from preclinical and clinical research indicates that synaptic plasticity is involved in the pathophysiology of mood disorders, and that many of the factors related to mood disorders including antidepressants, mood stabilizers, monoamine systems, hormonal changes, neurotrophin, cytokines, and electroconvulsive therapy have both direct and indirect effects on synaptic plasticity. Given that BPD is such a complex disease, it is not surprising that many molecules involved in the network of signaling cascades that regulate synaptic plasticity play a role in its pathophysiology.

The data reviewed in this chapter summarize the possible molecular mechanisms whereby biological or environmental stimulants enhance glutamatergic synaptic strength in the hippocampus or PFC, and how this correlates with mood-associated behaviors. In contrast, biological or environmental stimulants lead to decreased synaptic strength in the hippocampus, and this correlates with depressive-like behaviors. For example, increased serotonin, norepinephrine, dopamine, BDNF, acute corticosterone, and antidepressants lead to enhanced synaptic strength in the hippocampus and also correlate with antidepressant-like behaviors. However, inhibiting monoaminergic signaling and long-term stress weaken glutamatergic synaptic strength in the hippocampus and are associated with depressive-like symptoms.

Therefore, we propose the synaptic plasticity model as a convergent mechanism for mood disorders. However, many questions remain to be answered in this research area: (1) does this consistent correlation between synaptic plasticity and hippocortical path to mood-associated behaviors provide sufficient evidence to serve as a convergent biological mechanism? and (2) does the convergent biological mechanism provide a new avenue for drug screening?

Given these findings, further research with medications that specifically affect synaptic plasticity is warranted. Furthermore, more direct targeting of synaptic plasticity might be a strategy for the treatment of BPD, as this strategy would bypass defects in critical circuits required for monoaminergic antidepressants to exert their therapeutic effects. This line of research holds considerable promise and might lead to the next generation of rapid-acting antidepressants and antimanic agents, which could help to reduce the initial morbidity and mortality associated with this disorder.

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