Excitatory and inhibitory synaptic dysfunction in mania: an emerging hypothesis from animal model studies

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Abstract
Bipolar disorder (BD) is a common psychiatric disorder characterized by recurrent mood swings between depression and mania, and is associated with high treatment costs. The existence of manic episodes is the defining feature of BD, during which period, patients experience extreme elevation in activity, energy, and mood, with changes in sleep patterns that together severely impair their ability to function in daily life. Despite some limitations in recapitulating the complex features of human disease, several rodent models of mania have been generated and characterized, which have provided important insights toward understanding its underlying pathogenic mechanisms. Among the mechanisms, neuronal excitatory and inhibitory (E/I) synaptic dysfunction in some brain regions, including the frontal cortex, hippocampus, and striatum, is an emerging hypothesis explaining mania. In this review, we highlight recent studies of rodent manic models having impairments in the E/I synaptic development and function. We also summarize the molecular and functional changes of E/I synapses by some mood stabilizers that may contribute to the therapeutic efficacy of drugs. Furthermore, we discuss potential future directions in the study of this emerging hypothesis to better connect the outcomes of basic research to the treatment of patients with this devastating mental illness.

Introduction
Bipolar disorder (BD) is a common and devastating mental illness, characterized by recurrent mood swings between depression and mania with intervening euthymic states1. BD affects approximately 1–2.5% of the world’s population2, and the World Health Organization recognizes BD as the sixth leading cause of disability. Existence of manic episodes is the defining feature of BD, which differentiates it from unipolar major depressive disorder. The symptoms of manic episode include hyperactivity, impulsivity, elevated mood, inflated self-esteem, reduced anxiety, decreased need for sleep, and sometimes psychosis1. Both environmental and genetic risk factors contribute to the pathogenesis of mania, but the detailed molecular and cellular pathways underlying mania remain largely unknown.

So far, several rodent models of mania have been generated and characterized. Traditionally, pharmacological (e.g., psychostimulant amphetamine-induced) and environmental (e.g., sleep deprivation-induced) models were studied, but more recently various genetic models (i.e., knockout (KO), knock-in (KI), and overexpressing transgenic (TG) mice) have been developed3. Even with some limitations in satisfying all three (construct, face, and predictive) validities as a disease model3, 4, each of these rodent models has provided important insights toward understanding the pathogenic mechanisms of mania. For example, manic-like behaviors of rodents injected with amphetamine or those expressing lower levels of dopamine transporter3, together with clinical evidence of higher dopamine levels during manic episodes5, supported hyperdopaminergic activities as a major pathophysiology of mania. Nevertheless, the clinical
heterogeneity of mania, such as the differential response to certain pharmacological treatments\(^6\), suggests the possibility that other pathogenic mechanisms can still exist.

Neuronal excitability is tightly controlled by excitatory and inhibitory (E/I) synaptic balance, and dysfunction of this process has been strongly associated with numerous neurodevelopmental and neuropsychiatric disorders, including autism spectrum disorders (ASDs), intellectual disability (ID), and schizophrenia (SCZ)\(^7\)\(^{-}\)\(^10\). This could involve various underlying mechanisms ranging from abnormal expression and function of pre- or postsynaptic molecules\(^11\) to impaired maturation of certain neuronal cell types, such as \(\gamma\)-aminobutyric acid (GABA)ergic inhibitory interneurons\(^12\). Despite some evidence suggesting abnormal GABAergic interneurons in BD\(^13\), E/I synaptic dysfunction in mania has been relatively unexplored compared to that in other brain disorders. In the current review, we highlight recent studies of rodent manic models with impairments in E/I synaptic development and function. We also summarize thus far identified molecular and functional changes of E/I synapses by some mood stabilizers. Lastly, we discuss current limitations and potential future directions of this emerging hypothesis to better connect the outcomes of basic research to the treatment of patients with BD. For more general and comprehensive coverage of animal models of mania, we refer to recent excellent reviews\(^3\)\(^,\)\(^14\).

**Animal models of mania with E/I synaptic dysfunction**

**Shank3-overexpressing TG mice**

The SH3 and multiple ankyrin repeat domains 3 (SHANK3, also called PROSAP2) gene encodes a core scaffold protein in postsynaptic density (PSD) of the excitatory synapse\(^15\). By interacting with hundreds of different molecules in PSD\(^16\)\(^,\)\(^17\), including membrane proteins, signaling molecules, and cytoskeletal components, Shank3 organizes the macromolecular protein complex and is critically involved in proper development and function of excitatory synapses. Clinically, deletions and duplications of the chromosomal region (22q13) containing SHANK3 and various point mutations of SHANK3 have been identified in patients with ASDs, ID, SCZ, BD, and attention deficit hyperactivity disorder (ADHD)\(^18\)\(^,\)\(^19\). Han et al.\(^16\) recently identified two patients with small 22q13 duplications that likely include only SHANK3, and found that these patients were diagnosed with hyperkinetic disorders, BD, and ADHD, respectively. Notably, the symptoms of the patient with ADHD were not improved by treatment with amphetamine, a common medication for ADHD, suggesting the possibility that the disorder could not be typical ADHD, but more likely BD. To model SHANK3 duplications, Han et al. generated Shank3 TG mice that mildly overexpress Shank3 proteins (to approximately 150%) compared to wild-type (WT) mice. Indeed, the Shank3 TG mice displayed several manic-like behaviors, including locomotor hyperactivity and hypersensitivity to amphetamine in the open-field test (OFT), reduced despair-like behavior in the tail-suspension test (TST), increased acoustic startle response, reduced prepulse inhibition (PPI), and abnormal circadian rhythms, some of which responded to valproate (VPA), a Food and Drug Administration (FDA)-approved mood stabilizer and anticonvulsant for the treatment of manic or mixed episodes in BD\(^6\)\(^,\)\(^16\).

The E/I synaptic morphology and function of Shank3 TG mice were characterized mainly in the hippocampus\(^16\). The number of excitatory synapses was increased, while that of inhibitory synapses was decreased in the cultured hippocampal neurons of Shank3 TG mice compared to WT neurons. Functionally, amplitude, but not frequency, of spontaneous excitatory postsynaptic currents (sEPSCs) was significantly increased, while frequency, but not amplitude, of miniature inhibitory postsynaptic currents (mIPSCs) was decreased in the CA1 pyramidal neurons of acute hippocampal slices from Shank3 TG mice. Consistent with the shifted E/I synaptic balance toward more excitation but less inhibition, the Shank3 TG mice displayed abnormal electroencephalography (EEG) patterns in the frontal cortex and hippocampus, and exhibited spontaneous seizures. The abnormal EEG was also rescued by VPA treatment. At the molecular level, Han et al. found that Shank3 interacted with various actin-regulatory proteins to promote actin polymerization in the excitatory postsynaptic sites, thereby increasing the number of dendritic spines in the CA1 pyramidal neurons of Shank3 TG mice\(^6\)\(^,\)\(^20\).

It was unexpected that increased expression of Shank3 proteins that exclusively localize to excitatory, but not inhibitory, postsynaptic sites caused reduced number and function of inhibitory synapses in the Shank3 TG hippocampus. One possible explanation would be impaired maturation and/or function of GABAergic inhibitory neurons. However, Lee et al. recently showed that the densities of parvalbumin (PV)- and somatostatin-positive interneurons were normal in the hippocampus, striatum, and medial prefrontal cortex (mPFC) of Shank3 TG mice\(^21\). Therefore, it is more likely that the inhibitory synaptic changes observed in Shank3 TG mice could be due to the cell-autonomous postsynaptic changes of principal neurons that may involve a shift in distribution of certain actin-regulatory proteins, such as Mena and Profilin2, from inhibitory to excitatory postsynaptic sites\(^6\).

Despite the abnormal EEG in the frontal cortex of Shank3 TG mice, it remains to be directly investigated whether the E/I synaptic morphology and function are
also altered in other brain regions, such as the striatum and mPFC, of the mice. In this regard, it is notable that in the several lines of Shank3 KO and KI mice modeling ASDs and SCZ, changes in the number and function of E/I synapses in these brain regions have been observed. Moreover, Lee et al. recently showed increased levels of actin filaments (F-actin) in the striatum of Shank3 TG mice, similar to the hippocampus. The detailed mechanism of how VPA treatment rescued the manic-like behaviors of Shank3 TG mice is also unknown. One possibility is that VPA enhanced the GABAergic inhibitory synaptic transmission of Shank3 TG mice by inhibiting a GABA-catabolizing enzyme, GABA transaminase, and thereby normalizing the E/I synaptic balance.

**Forebrain-specific Plcg1 KO mice**

Phospholipase Cy1 (PLCy1) is an enzyme that, when activated by receptor tyrosine kinases, hydrolyzes membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP2) to generate the second messengers diacylglycerol and inositol-1,4,5-triphosphate (IP3). In neurons, brain-derived neurotrophic factor (BDNF), through its receptor tropomyosin receptor kinase B (TrkB), activates PLCy1 together with other downstream signaling components, including Ca2+/calmodulin-dependent protein kinase II (CaMKII), extracellular signal-regulated kinase, and cAMP response element-binding protein to regulate synaptic development, function, and plasticity. Despite some studies suggesting the association between PLCG1 polymorphism and BD, the functional roles of PLCy1 in mature neurons in vivo have not been investigated because of the lethality of conventional Plcg1 KO mice at an early embryonic stage. To solve this problem, recently, Yang et al. generated forebrain-specific Plcg1 KO mice by crossing the floxed Plcg1 mice with CaMKII-Cre mice (Plcg1fl/fl; CaMKII mice). The Plcg1fl/fl; CaMKII mice exhibited several manic-like behaviors, including locomotor hyperactivity in the OFT, reduced anxiety-like behavior in the elevated plus maze (EPM) test, reduced despair-like behavior in the forced swim test (FST), hyperhedonic behavior in the sucrose preference test (SPT), and increased acoustic startle response, many of which were normalized by treatment with VPA or lithium, another FDA-approved mood stabilizer for the treatment of mania in BD. In addition to the manic-like behaviors, the mice showed impaired learning and memory in the auditory and contextual fear conditioning tests.

The basal excitatory synaptic transmission of Plcg1fl/fl; CaMKII mice was normal in the hippocampal Schaffer collateral (SC)-CA1 synapses as measured by the input-output relationship and the N-methyl-D-aspartic acid (NMDA) receptor to α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor current ratio (NMDAR/AMPA ratio). Moreover, amplitude and frequency of miniature EPSCs (mEPSCs) were normal in the CA1 pyramidal neurons of Plcg1fl/fl; CaMKII mice. Consistently, expression levels of several excitatory synaptic proteins and number of dendritic spines in the hippocampus of Plcg1fl/fl; CaMKII mice were comparable to those of WT mice. In contrast, the Plcg1fl/fl; CaMKII mice showed defects in the inhibitory synapses of the hippocampus and dorsal striatum. Specifically, frequency, but not amplitude, of mIPSCs in the CA1 pyramidal neurons was reduced in the hippocampal slices of Plcg1fl/fl; CaMKII mice compared to WT mice. Notably, in the dorsal striatum, where D1 (dopamine receptor D1-expressing) and D2 (dopamine receptor D2-expressing) type medium spiny neurons (MSNs) accounted for the majority (>90%) of the neuronal population, the amplitude of mIPSCs was reduced only in the D1 type, but not D2 type, MSN of Plcg1fl/fl; CaMKII mice. This is somewhat consistent with the behavioral phenotype of the mice, as activation of D1-type MSN promotes locomotor activities.

These functional defects of inhibitory synapses were explained by a reduced number of GABAergic inhibitory presynaptic terminals on the principal neurons. At the molecular level, both basal and BDNF-induced phosphorylation of CaMKIIα were significantly decreased at the inhibitory postsynaptic sites of Plcg1fl/fl; Nestin cultured hippocampal neurons. Furthermore, the surface expression of inhibitory GABA_A receptor α1 subunit, which is known to be regulated through its phosphorylation by CaMKIIα, was also decreased in the Plcg1fl/fl; Nestin hippocampal neurons compared to WT neurons.

In addition to the E/I synaptic dysfunction in the hippocampus and striatum, BDNF-TrkB-dependent long-term potentiation, a type of synaptic plasticity, at the SC-CA1 synapses of Plcg1fl/fl; CaMKII hippocampus was also defective, which could explain the impaired learning and memory of the mice. Together, these findings suggest that BDNF-TrkB-PLCγ1 signaling is required for the proper development and function of inhibitory synapses and for the normal synaptic plasticity in the striatum and hippocampus, defects of which contribute to manic-like behaviors and impaired learning and memory in the forebrain-specific Plcg1 KO mice.

**Ank3-1b heterozygous mice**

The ANKRYIN 3 (ANK3) gene encodes multiple isoforms of Ankyrin-G proteins that link membrane proteins to the β-spectrin/actin cytoskeleton and thereby organizing macromolecular complexes at the specialized plasma membrane compartments. In neurons, Ankyrin-G proteins are involved in the formation and maintenance of axon initial segments (AISs) and node of Ranvier, membrane compartments critical for action potential generation and propagation, where they connect several
ion channels to the cytoskeleton. Notably, the ANK3 gene has been repeatedly associated with BD from several large-scale genome-wide association studies.

Recently, Leussis et al. generated two different mouse models with reduced Ank3 expression and found that both showed some manic-like behaviors. In the first model, Ank3 expression was specifically reduced in the hippocampal dentate gyrus (DG) using the lentivirus expressing short hairpin RNAs targeting Ank3. These mice showed reduced anxiety-like behavior in multiple behavioral assays, including the EPM, light-dark transition, and novelty-suppressed feeding tasks. In addition, the mice showed increased home-cage activity during the light, but not the dark, phase. Both reduced anxiety-like behavior and increased activity were rescued by treatment with lithium. The second model was generated by disrupting the exon 1b locus of Ank3 (Ank3-1b), which resulted in decrease of the Ankyrin-G isoforms containing exon 1b in several brain regions, including the DG, cortex, and cerebellum. Because of the progressive early-onset ataxia in homozygous Ank3-1b−/− mice, the behavioral phenotypes of heterozygous Ank3-1b+/− mice were characterized and compared to those of WT mice. Similar to the mice with DG-specific decrease of Ank3 expression, Ank3-1b+/− mice displayed reduced anxiety-like behavior in the EPM, light-dark transition, and novelty-suppressed feeding tasks. Moreover, Ank3-1b+/− mice exhibited hyperhedonic behavior in the SPT. Intriguingly, after chronic social isolation stress, the manic-like behaviors of Ank3-1b+/− mice were shifted to depression-like behaviors. Specifically, singly housed Ank3-1b+/− mice showed increased anxiety-like behavior in the EPM test, anhedonic behavior in the SPT, and despair-like behavior in the FST, compared to singly housed WT mice. This elevated susceptibility to stress of Ank3-1b+/− mice was partly explained by the higher plasma levels of corticosterone compared to WT mice, both under basal and acute stress conditions.

Alternative first exons (1a/1a’, 1e, and 1b) of ANK3 gene encode distinct N-terminal peptide sequences of Ankyrin-G isoforms. Importantly, Lopez et al. revealed that PV-positive GABAergic inhibitory interneurons express only Ankyrin-G isoforms containing exon 1b, while excitatory principal neurons express the isoforms containing either exon 1e alone, or both 1e and 1b. Consistently, clustering of voltage-gated sodium channels at the AISs of PV-positive interneurons was significantly decreased in Ank3-1b+/− mice compared to WT mice. Further supporting the interneuron dysfunction, Ank3-1b+/− and Ank3-1b−/− mice exhibited abnormal EEG and seizures in an Ank3 gene dose-dependent manner (i.e., they were more severe in homozygous Ank3-1b−/− than in heterozygous Ank3-1b+/− mice). In addition, the detailed electrophysiological analysis showed reduced intrinsic excitability of the PV-positive interneurons in Ank3-1b+/− mice compared to WT mice. Combining the abovementioned studies, it is conceivable that functional changes of PV-positive GABAergic inhibitory neurons and their synapses in some brain regions of Ank3-1b+/− mice could contribute to manic-like behaviors.

More recently, Zhu et al. generated and characterized a mouse model with conditional disruption of Ank3 in pyramidal neurons of adult forebrain (Ank3Δ/−; CaMKII). All three major isoforms of Ankyrin-G proteins (190, 270, and 480 kDa) were decreased in the forebrain regions of Ank3Δ/−; CaMKII mice. These mice, similar to Ank3-1b+/− mice, displayed several manic-like behaviors responsive to lithium and VPA, which could be shifted to depression-like behaviors after repeated social defeat stress. There was a loss of sodium and potassium channels at AISs of pyramidal neurons in Ank3Δ/−; CaMKII mice. Moreover, the number of inhibitory synapses innervating pyramidal neuron AISs was significantly decreased in the cortex of Ank3Δ/−; CaMKII mice. Consistent with disinhibition, c-fos expression was increased in cortical pyramidal neurons of the mice, indicating increased cortical activity. Therefore, both Ank3-1b+/− and Ank3Δ/−; CaMKII mice have some defects in the inhibitory synaptic function. Nevertheless, in addition to the AISs, Ankyrin-G proteins also localize to the dendritic spines of glutamatergic excitatory postsynapse where they regulate dendritic spine morphology, and excitatory synaptic transmission and plasticity. Therefore, morphological and functional changes of excitatory synapses in some brain regions of Ank3-1b+/− and Ank3Δ/−; CaMKII mice cannot be excluded, details of which remain to be investigated.

Clock19 mutant mice

Abnormalities in circadian rhythms and sleep disturbance have been linked with BD and manic episodes. The circadian locomotor output cycles kaput (CLOCK) gene encodes a CLOCK protein that forms a heterodimer with brain muscle ARNT-like 1 (BMAL 1) and functions as a critical transcriptional regulator in the feedback network of the molecular clock. Notably, polymorphisms of CLOCK and BMAL 1 have been associated with BD. The Clock19 mutant mice have N-ethyl-N-nitrosourea-induced single base mutation at the 5’ splice donor site of intron 19, which results in loss of exon 19 during splicing and thereby produces a dominant negative CLOCK protein. Indeed, Clock19 mutant mice show significant circadian rhythm defects both in the molecular and behavioral levels.

McClung’s group has reported a series of studies demonstrating the manic-like behaviors of ClockΔ19 mutant mice and revealing the underlying molecular and neural circuit mechanisms.
exhibited locomotor hyperactivity both in novel and familiar environments, increased response to various reward stimuli, hyperhedonic behavior in the SPT, reduced despair-like behavior in the FST, and reduced anxiety-like behavior in the EPM test, some of which were rescued by treatment with lithium\textsuperscript{54–56}. Intriguingly, the manic-like behaviors of Clock\textsuperscript{19} mutant mice were time-dependent; the behaviors were significant during the day time, but were normalized to WT levels (euthymic states) during the night time\textsuperscript{57}. Hyperdopaminergic activity due to the increased firing rate of dopaminergic neurons in the ventral tegmental area (VTA) was shown as a key neuronal mechanism for the manic-like behaviors of Clock\textsuperscript{19} mutant mice\textsuperscript{55}. Specifically, viral expression of functional CLOCK proteins in the VTA of mutant mice was sufficient to rescue the manic-like behaviors\textsuperscript{54}. Moreover, the dopaminergic neuron firing rate, tyrosine hydroxylase expression, and dopamine synthesis in the VTA of mutant mice coincided with the time-dependent behavioral changes\textsuperscript{57}.

The nucleus accumbens (NAc) is a brain region of the ventral striatum critically involved in mood, reward, and addiction-related behaviors, and the MSNs of NAc get dopaminergic inputs from the VTA and excitatory glutamatergic inputs from the prefrontal cortex\textsuperscript{58}. The hyperdopaminergic activity of Clock\textsuperscript{19} mutant mice could lead to the circuit level changes of NAc and thereby contribute to the manic-like behaviors. Indeed, Dzirasa et al.\textsuperscript{59} revealed neurophysiological abnormalities of the NAc microcircuits in Clock\textsuperscript{19} mutant mice by performing simultaneous in vivo extracellular recordings from the VTA, NAc, and prefrontal cortex. Specifically, low-gamma oscillations and single neuron phase coupling were defective in the NAc of Clock\textsuperscript{19} mutant mice, which were normalized by treatment with lithium. At the molecular level, total-, phospho (S845)-, and surface expression levels of the GluA1, but not the GluA2, subunit of AMPA receptors were decreased in the NAc of mutant mice compared to WT mice, suggesting that increased dopamine release may indirectly lower the excitatory synaptic transmission of NAc in Clock\textsuperscript{19} mutant mice\textsuperscript{55,59,60}. Consistent with the biochemical changes, mEPSC amplitude, but not frequency, and AMPAR/NMDAR ratio were decreased in the MSNs of Clock\textsuperscript{19} mutant NAc\textsuperscript{60}. Furthermore, viral-mediated overexpression of the GluA1 subunit of the AMPA receptor in the NAc was sufficient to normalize some manic-like behaviors of the mutant mice, including reduced anxiety-like behavior in the EPM test and increased reward sensitivity in the conditioned place preference test\textsuperscript{60}.

Together, reduced excitatory synaptic function of the MSNs in NAc, potentially as a consequence of increased activity of dopaminergic inputs from the VTA, could be an important mechanism for the manic-like behaviors of Clock\textsuperscript{19} mutant mice. It remains to be investigated whether the inhibitory synapses of MSNs in Clock\textsuperscript{19} mutant mice have also any molecular and functional changes. Moreover, whether the E/I synapses of D1- and D2-type MSNs could be differentially altered in the mutant mice is an interesting topic for future research\textsuperscript{61}.

**Sleep-deprived animals**

Clinically, reduced sleep or sleep disturbances can trigger and worsen manic episodes\textsuperscript{62}. Similarly, sleep deprivation protocols, usually obligating rodents to remain awake on a small platform surrounded by water for an extended period of time (72 h), have long been used to generate manic models\textsuperscript{63}. The sleep-deprived animals indeed exhibit several manic-like behaviors, including locomotor hyperactivity, aggressive behavior, hyposexuality, and increased stereotypy, which could be normalized by treatment with lithium\textsuperscript{63,64}.

A few studies have suggested that protein kinase C (PKC) could mediate important molecular mechanisms underlying the manic-like behaviors of sleep-deprived animals. The levels of PKC activity and phosphorylation of some PKC substrates were increased in the frontal cortex of sleep-deprived rats\textsuperscript{65}. Moreover, treatment of quercetin, a PKC inhibitor, prevented sleep deprivation-induced locomotor hyperactivity in mice\textsuperscript{66}. Among the increased PKC-dependent phosphorylation by sleep deprivation, those on the S896 of the GluN1 subunit of the NMDA receptor and the T840 of the GluA1 subunit of the AMPA receptor are notable\textsuperscript{65}. S896 phosphorylation of GluN1 is involved in regulating intracellular trafficking and surface expression of NMDA receptors\textsuperscript{67}. T840 phosphorylation of GluA1 could enhance channel conductance of AMPA receptors\textsuperscript{68}. Therefore, it is possible that sleep deprivation could affect excitatory synaptic function and plasticity in the frontal cortex, which then contribute to manic-like behaviors.

Sleep deprivation-induced alterations in synaptic function and plasticity have been extensively investigated in different brain regions of rodents, although, in many of the studies, behavioral changes after various sleep deprivation protocols were not characterized, and therefore the synaptic changes may not be directly associated with mania. In the CA1 and DG neurons of the hippocampus, sleep deprivation resulted in impairment of long-term potentiation\textsuperscript{69,70}. Consistent with the notion that NMDA receptors are critical upstream regulators of synaptic plasticity\textsuperscript{71}, surface expression of NMDA receptors and NMDA receptor-mediated currents were reduced after sleep deprivation\textsuperscript{72,73}. Meanwhile, AMPA receptor function, as measured by mEPSCs, was normal in the hippocampus\textsuperscript{73}. Impaired hippocampal long-term potentiation, nevertheless, could be more associated with learning and
| Mood stabilizer | E/I synaptic changes | Species and brain regions | References |
|----------------|----------------------|---------------------------|------------|
| Lithium        | **Molecular**        |                           |            |
|                | Increases synaptic expression of AMPAR GluA2 subunit | Mouse HIP and rat cultured HIP neurons | 89         |
|                | Increases synaptic clustering of gephyrin | Rat cultured HIP neurons | 90         |
|                | Increases synaptic expression of GABA<sub>B</sub>R | Rat frontal CTX | 91         |
|                | Decreases mRNA levels of Homer1b/c and Shank1 | Rat CTX and STR | 92         |
|                | Decreases surface expression of AMPAR GluA1 subunit | Mouse cultured HIP neurons | 93         |
|                | Decreases tyrosine phosphorylation of NMDAR NR2A subunit | Rat HIP | 94         |
|                | Decreases tyrosine phosphorylation of NMDAR NR2B subunit | Rat cultured CTX neurons | 95         |
|                | Decreases synaptosomal and surface expression of AMPAR GluA1 and GluA2 subunits | Rat HIP and cultured HIP neurons | 96–98      |
|                | **Morphological**    |                           |            |
|                | Increases number of excitatory synapses | Rat cultured HIP neurons | 99         |
|                | Increases number of dendritic spines in Dixdc1 KO mice | Mouse primary somatosensory CTX | 100        |
|                | Decreases number of dendritic spines in fmr1 KO mice | Mouse mPFC | 101        |
|                | **Functional**       |                           |            |
|                | Increases AMPAR opening probability | Rat HIP | 102        |
|                | Increases input-output relationship and long-term potentiation | Rat DG | 103        |
|                | Increases excitatory presynaptic transmission | Rat HIP | 104, 105   |
|                | Decreases AMPAR/NMDAR ratio | Rat HIP | 97         |
|                | Decreases amplitude of AMPAR-mediated mEPSC | Mouse cultured HIP neurons | 93         |
|                | Decreases long-term depression | Rat HIP | 106        |
| Valproate      | **Molecular**        |                           |            |
|                | Increases level of GABA and activity of GAD | Mouse whole brain | 107        |
|                | Increases GABA but decreases glutamate levels | Mouse whole brain | 108        |
|                | Increases levels of glutamate transporters and capacity of glutamate uptake | Rat HIP | 109        |
|                | Decreases mRNA levels of Homer1b/c and Shank1 | Rat CTX and STR | 92         |
|                | Decreases synaptosomal and surface expression of AMPAR GluA1 and GluA2 subunits | Rat HIP and cultured HIP neurons | 96–98      |
|                | **Morphological**    |                           |            |
|                | Increases number of dendritic spines in prenatal VPA-induced ASD model mice | Mouse HIP | 110        |
|                | **Functional**       |                           |            |
|                | Increases GABA-induced inhibition in single unit recording | Rat CTX | 111        |
|                | Decreases amplitude of NMDAR-mediated EPSP | Rat AMYG | 112        |
|                | Decreases NMDAR-mediated EPSP slope but increases GABAR-mediated IPSP slope | Rat HIP | 113        |
|                | Decreases amplitude of non-NMDAR-mediated EPSP | Rat HIP | 114        |
| Lamotrigine    | **Molecular**        |                           |            |
|                | Increases surface expression of AMPAR GluA1 and GluA2 subunits | Rat cultured HIP neurons | 98         |
memory deficits after sleep deprivation than with manic-like behaviors. In the frontal cortex, mild sleep deprivation increased mEPSC amplitude and frequency of layer II/III pyramidal neurons. In the deep layers (V/VI) of the mPFC, sleep deprivation decreased amplitude, but not frequency, of mEPSCs without affecting the properties of mIPSCs. Together, sleep deprivation could result in diverse changes of E/I synaptic function, depending on the brain regions and sleep deprivation protocols. Therefore, more investigations are necessary to understand the causal relationship between E/I synaptic changes of certain brain regions and manic-like behaviors after sleep deprivation.

**Molecular and functional changes of E/I synapses by mood stabilizers**

Clinically, antipsychotics (such as haloperidol, risperidone, and olanzapine) and mood stabilizers (such as lithium, VPA, lamotrigine, and carbamazepine) are most commonly used for the acute and long-term management of mania, respectively. Antipsychotics exhibit high-affinity antagonism toward dopamine and serotonin receptors, but their chronic treatment could also affect glutamate receptor expression. The molecular targets and mechanisms of action for mood stabilizers are more complex than those for antipsychotics, and there are still many questions remaining in the field. For example,
lithium alone has multiple direct targets, including inositol monophosphatase, phosphoglucomutase, and glyco-gen synthase kinase-3, and additionally affects diverse downstream pathways indirectly\(^{26,79}\).

In Table 1, we summarize animal model and in vitro-cultured neuron studies showing E/I synaptic changes by mood stabilizers, at the molecular, cellular, and functional levels. It is notable that possibly depending on the treatment and measurement conditions, synaptic changes in a certain brain region by a single mood stabilizer can be diverse, or even opposite. Therefore, further investigations are necessary to understand whether and to what extent each of these synaptic changes contributes to the therapeutic efficacy of drugs.

Conclusions and prospects

As we summarized in this review, there is an increasing number of evidence supporting the pathogenic role of E/I synaptic dysfunction in mania (Fig. 1). Nevertheless, there are many limitations and questions remaining from animal model studies. First, brain regions, neural circuits, and neuronal cell types mediating specific behavioral phenotypes of mania need to be further dissected. For example, locomotor hyperactivity and hyperhedonic behavior may be mediated by synaptic changes of different brain regions, such as the dorsal striatum and NAc, respectively\(^{35,58}\). Recent advances in viral-mediated gene delivery combined with optogenetic tools and brain-clearing technology have revealed the structural and functional anatomy of neural circuits critical for several depression-related behaviors\(^{80,81}\). Similar approaches could be applied to the abovementioned animal models of mania to test whether activation or inhibition of specific neural circuits could rescue a subset of behavioral phenotypes. Second, E/I synaptic changes preceding the onset of behavioral phenotypes may be identified and the effect of preventing such earlier synaptic changes could be investigated. In most studies so far, morphological and functional changes of the E/I synapses have been characterized at the ages when the manic-like behaviors of animal models are fully developed. Therefore, it is possible that those E/I synaptic changes may include some compensatory and homeostatic responses of neurons and/or neural circuits, and, thus, could not be causally associated with the behavioral phenotypes. Notably, in the case of schizophrenia, earlier intervention during the juvenile stage has shown to prevent adult onset of behavioral deficits in animal models\(^{82}\). Third, E/I synaptic mechanisms underlying the differential responses to certain mood stabilizers could be investigated using animal models. Although lithium still remains the first-line treatment for BD, only about 30% of BD patients show full responses to lithium treatment\(^{83}\). Despite the poorly defined neurobiological mechanism, a few genome-wide association studies have linked the variants of genes functioning in the E/I synapses, such as GRIA2 (for the glutamate receptor, ionotropic, AMPA2) and GADLI (for the glutamate decarboxylase-like 1), to the differential responses to lithium treatment\(^{84,85}\). In this regard, it is intriguing that the manic-like behaviors of Shank3 TG mice were selectively rescued by VPA, but not by lithium\(^{86}\). More comprehensive analysis of behavioral and synaptic changes in the animal models of mania after single or mixed treatment with various drugs for BD will be an interesting direction of future study. Last but not least, the animal model studies need to be converged with clinical research on patients\(^{86}\). Advances in neuroimaging and induced pluripotent stem cell technologies have already narrowed the gaps between the preclinical and clinical studies of BD\(^{87,88}\), which, when combined, will provide important insights toward understanding the pathophysiology and potential treatment of this complex and heterogeneous mental illness.

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Conflict of interest

The authors declare that they have no conflict of interest.

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