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Variants in Ion Channel Genes Link Phenotypic Features of Bipolar Illness to Specific Neurobiological Process Domains

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Key Words

Bipolar disorder · Genetic load · Phenome · Voltage-gated ion channels · Impulse control · Cognitive deficits · Circadian rhythm · Energy disturbances · Mood episodes · Neurobiological process domains · Environmental trigger

Abstract

Recent advances in genome-wide association studies are pointing towards a major role for voltage-gated ion channels in neuropsychiatric disorders and, in particular, bipolar disorder (BD). The phenotype of BD is complex, with symptoms during mood episodes and deficits persisting between episodes. We have tried to elucidate the common neurobiological mechanisms associated with ion channel signaling in order to provide a new perspective on the clinical symptoms and possible endophenotypes seen in BD patients. We propose a model in which the multiple variants in genes coding for ion channel proteins would perturb motivational circuits, synaptic plasticity, myelination, hypothalamic-pituitary-adrenal axis function, circadian neuronal rhythms, and energy regulation. These changes in neurobiological mechanisms would manifest in endophenotypes of aberrant reward processing, white matter hyperintensities, deficits in executive function, altered frontolimbic connectivity, increased amygdala activity, increased melatonin suppression, decreased REM latency, and aberrant myo-inositol/ATP shuttling. The endophenotypes result in behaviors of poor impulse control, motivational changes, cognitive deficits, abnormal stress response, sleep disturbances, and energy changes involving different neurobiological process domains. The hypothesis is that these disturbances start with altered neural circuitry during development, following which multiple environmental triggers may disrupt the neuronal excitability balance through an activity-dependent molecular process, resulting in clinical mood episodes.

Introduction

Bipolar disorder (BD) is a chronic illness with characteristic episodes of high and low activity and energy; these episodes affect the functioning of the individual, resulting in morbidity and mortality. BD has a heritability of about 80% and often affects multiple family members [1]. Meta-analyses of genome-wide association and gene expression studies have shown that ion channel genes and biological pathways involved in ion channel regulation are associated with BD [2–4].

Genome-wide association studies have shown strong evidence of an association of single nucleotide polymorphisms (SNP) within calcium channel genes with BD. The SNP rs100637 within the calcium channel gene *CACNA1C* (calcium channel, voltage-dependent, L type, alpha 1C subunit) is associated at a genome-wide level in

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mega-analyses incorporating all available BD genetic datasets (PGC BP Working Group, 2011, 2013). Similarly, SNPs in the calcium channel gene *CACNB2* (calcium channel, voltage-dependent, beta 2 subunit) and *CACNA1D* (calcium channel, voltage-dependent, L type, alpha 1D subunit), along with *CACNA1C*, showed genome-wide significance across major psychiatric disorders including BD [5]. SNPs in the calcium channel gene *CACNG2* (calcium channel, voltage-dependent, gamma 2 subunit) were also associated with BD in a study of the 22q region in a smaller sample [6], and SNPs in the gene region were also associated with lithium response [7]. Calcium channel genes as a group were associated with BD in gene set analyses by the PGC BP Working Group and the PGC Cross-Disorder Group [8, 9].

Another gene that contains SNPs showing strong evidence for an association with BD is *ANK3* [ankyrin 3, node of Ranvier (ankyrin G)] [10–12]. The *ANK3* gene codes for the scaffolding protein ankyrin-G, which stabilizes the position of sodium and potassium channels in the nerve cell membrane [13].

Evidence is accumulating that SNPs near the potassium channel genes *KCNQ2* (potassium voltage-gated channel, KQT-like subfamily, member 2) and *KCNQ3* (potassium voltage-gated channel, KQT-like subfamily, member 3) may also be associated with BD [14–17]. Recently, putatively damaging variants in the potassium channel genes *KCNH7* (potassium voltage-gated channel, subfamily H, member 7), *KCNG4* (potassium voltage-gated channel, subfamily G, member 4), and *KCNB2* (potassium voltage-gated channel, Shab-related subfamily, member 2) have been identified within a large Old Order Amish pedigree [18].

The estimated risk of bipolar illness for SNP rs10994397 in the *ANK3* gene is 1.17, for SNP rs4765913 in the *CACNA1C* gene 1.13, and for SNP rs11168751 in the *CACNB3* gene 0.84 [19]. The mechanism by which the risk variants (or nearby functional variants) in genes coding for ion channel proteins may alter the neurobiology and neural circuitry in persons with BD is not clearly understood. It could be hypothesized that these variants result in altered excitability, neurotoxicity, synaptic plasticity, and/or neurotransmitter signaling. Several review papers have addressed the neurobiology underlying the ion channel dysfunction in BD [20–22]. In this paper, we have tried to elucidate the common neurobiological mechanisms by which calcium, sodium, and potassium channel abnormalities might contribute to the clinical symptoms, including possible endophenotypes and the overall pathogenesis of BD.

Calcium, *ANK3*, and Potassium Channel Genes and Proteins

Ion channels regulate the balance between neuronal excitation and inhibition by conductance of ions in and out of the cell. The resting state membrane potential and the action potential in neurons are due to movement of sodium, potassium, and chloride ions across the membrane. An afterhyperpolarization phase following the action potential in neurons, which prevents hyperexcitability, is achieved by movement of a calcium current through various voltage-dependent calcium channels [23–26] and a K^+ current through potassium channels [27].

Voltage-gated calcium channels consist of a core alpha 1 subunit, which is the calcium sensor, along with other subunits (beta, alpha 2/delta, and gamma). The alpha 1 subunit consists of five families (L, P/Q, N, R, and T type) depending upon the voltage activation characteristics [28]. L-type voltage-dependent calcium channels (LTCC) consist of four members ($Ca_v1.1$, 1.2, 1.3, and 1.4) and are present in many tissues throughout the body, including the brain, ventricular myocytes, skeletal muscle, and vascular smooth muscle [29–32]. The *CACNA1C* gene, which maps to 12p13.3, encodes an alpha 1C subunit of an LTCC protein ($Ca_v1.2$). This is the major subunit in the brain and plays an important role in synaptic plasticity, dendritic structure, learning, and memory [22]. $Ca_v1.2$ proteins are concentrated near the cell body, proximal dendrites, and dendritic tree in the neurons, modulating gene transcription and signaling pathways and thereby altering neuronal excitability [22, 33–35]. The *CACNA1D* gene maps to chromosome 3p14.3; this gene codes for the alpha 1 delta subunit of the L-type voltage-gated calcium channel $Ca_v1.3$ [30]. The *CACNA1A* gene (calcium channel, voltage-dependent, P/Q type, alpha 1A subunit) maps to chromosome 19p13; it codes for the voltage-dependent alpha 1A subunit P/Q calcium channel $Ca_v2.1$ protein. $Ca_v2.1$ is expressed predominantly in the nervous system, and mutations in *CACNA1A* have been associated with familial hemiplegic migraines [36]. The *CACNA1B* gene maps to chromosome 9q34; it codes for the voltage-dependent alpha 1B subunit of the N-type calcium channel $Ca_v2.2$ protein and controls the channel activity of the alpha 1 subunit [37]. The *CACNB1–4* genes code for four beta subunits of the voltage-dependent calcium channel [38]. The beta subunit is essential for the stabilization of the alpha 1 subunit and can control the activation and inactivation of other voltage-gated calcium channel subunits [39–41]. The *CACNG1–8* genes code for eight gamma subunits of voltage-gated calcium

channels [42]. The gamma 2, 3, 4, and 8 subunits are called transmembrane AMPA receptor regulatory proteins, which are involved in the trafficking of AMPA receptors to the membrane in the synapse [43].

The *ANK3* gene maps to 10q21; it codes for two 480- and 270-kDa isoforms of a brain-specific protein called ankyrin-G, with the isoforms localized at the axon initial segment and at the nodes of Ranvier in the neuron, respectively [44]. Ankyrin-G binds to sodium and potassium channels at the axon initial segment and nodes of Ranvier and is essential for clustering of sodium channels [45–47] and potassium channels [48, 49].

The potassium channels fall into four families consisting of voltage-gated (K_v), inward-rectifying (K_{ir}), calcium-activated (K_{Ca}), and tandem pore domain (K_{2p} and 4T) channels [50]. The potassium channel genes *KCNQ2*, which maps to 20q13.3, and *KCNQ3*, which maps to 8q24, code for the voltage-gated potassium channel proteins termed K_v7.2 and 7.3. They form an integral part of the M potassium channel, slowly activating and deactivating the M current that regulates neuronal excitability [51, 52]. The *KCNB2* gene, which maps to 8q13.2, codes for the potassium channel protein K_v2.2, which is found in axon initial segments and dendrites of the medial nucleus of trapezoid body neurons and cortical pyramidal neurons and plays a role in regulating action potential amplitude and firing [53, 54]. The *KCNH7* gene, which maps to 2q24.2, codes for the voltage-gated subfamily member H subunit of potassium channel K_v11.3. This is present primarily in the nervous system and plays an important role in the regulation of the membrane potential and neuronal excitability [55].

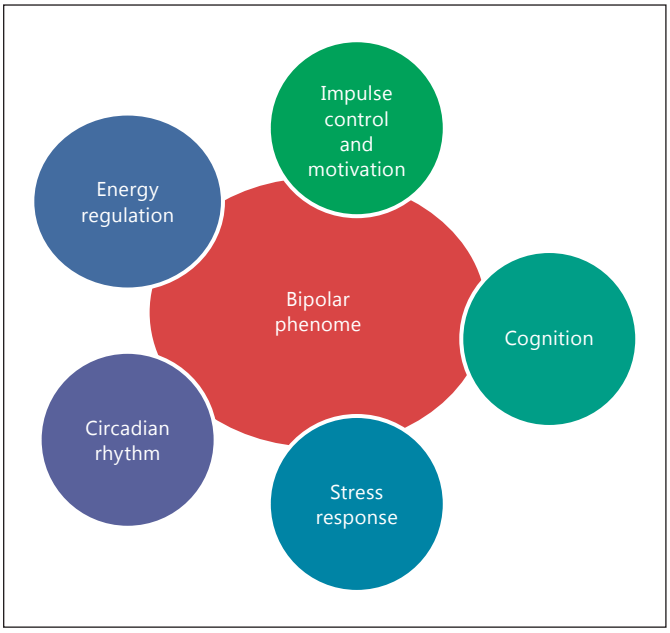

Fig. 1. Deconstructing bipolar symptoms into neurobiological process domains.

The Phenome of BD from the Ion Channel Perspective

A phenome represents the set of all phenotypes expressed at various levels, including manifestations at the cell, tissue, and organic level, representing the sum total of phenotypic traits. BD patients exhibit mood episodes that include poor impulse control, cognitive deficits, abnormal stress response, sleep disturbances, and fluctuations in energy level, along with mood states of mania, depression, and/or irritability including rapid switches from mania to depression and depression to mania; these symptoms and signs represent the phenome at the organic level. The clinical symptoms seen in bipolar illness patients could be deconstructed into neurobiological process domains of impulse control/motivational reward processing, cognition, stress response, circadian rhythm, energy regulation, and metabolism, representing the 'bipolar phenome' (fig. 1). Some abnormalities in the BD phenome may represent endophenotypes. Rieder and Gershon [56] proposed that a genetic vulnerability marker should be heritable, associated with illness, state independent, and cosegregate with illness within families. Gottesman and Gould [57] first used the term 'endophenotype' to describe such biomarkers. Besides the criteria above, they proposed that the endophenotype should occur with a higher incidence in nonaffected family members than in the general population. Possible endophenotypes in BD have been described in several reviews [58, 59].

We are suggesting that the following characteristics related to BD may be candidate endophenotypes: motivational reward processing, white matter hyperintensities, deficits in executive function, altered frontolimbic connectivity, aberrant amygdala activity, melatonin suppression, REM latency, and myo-inositol/ATP shuttling [58, 60]. We posit that these are present even before the mood episodes emerge and that the genetic load of SNPs, structural variants, and sequence variants affecting ion channel genes contributes to those deficits starting early in development. Below, we elucidate the neurobiological mechanisms underlying calcium, sodium, and potassium

ion channel signaling and relate these mechanisms to the phenome, including possible endophenotypes and the clinical symptomatology of BD.

Impulse Control and Motivational Reward Processing

Patients with BD exhibit poor impulse control, resulting in impulsive risk-taking behaviors and addiction to substances [61]. Clinical studies using the Barratt Impulsiveness Scale (BIS) have shown that impulsivity is present not only during affective states but also in the euthymic state [62, 63], and that it also occurs in unaffected siblings [64]. Lombardo et al. [64] studied impulsivity using the BIS-11 in euthymic bipolar patients, unaffected relatives, and healthy controls. The BIS-11 scores were higher in unaffected relatives during motor and nonplanning tasks than in controls. Euthymic bipolar patients showed a higher score in all subgroups of attention, motor, and nonplanning tasks compared to unaffected relatives and controls, indicating that poor impulse control might be an endophenotype of bipolar illness. A study involving the Iowa Gambling Task in bipolar patients has shown that their performance was significantly impaired, with patients making erratic choices both in euthymic and ill states [65]. Motivational reward-related behavioral tasks and functional imaging studies have shown dysfunctional reward learning in BD patients irrespective of their state [66, 67]. Functional MRI (fMRI) studies in unaffected relatives showed an increased activation of the orbitofrontal cortex and amygdala in response to reward-related stimuli [68].

How may ion channel dysfunction contribute to poor impulse control and motivational reward processing? Mesolimbic and mesocortical dopaminergic circuits have been implicated as key networks in impulse control and motivational reward processing [69, 70]. The neurobiological mechanisms that regulate dopaminergic neuron firing and dopamine release in mesolimbic and mesocortical circuits would lead to poor impulse control and motivational reward processing. Ferrari et al. [71] have shown that mouse pup brains show spontaneous bursting in midbrain dopamine neurons (which send axonal projections to the striatum) at the E16 embryonic stage; this bursting is regulated by L- and N-type calcium channels, which release dopamine based on stimulation in a calcium-dependent manner. Velazquez-Ulloa et al. [72] have shown that manipulating the calcium spike in the developing *Xenopus* larva can alter the number and specification of dopaminergic neurons in different brain regions. They altered the calcium spike by injecting constructs of the inward-rectifying potassium channel $K_{ir}2.1$ or the sodium channel Na_v2a αβ into the embryos; this resulted in variable dopaminergic neuron expression depending upon the location. Soden et al. [73] showed that introduction of the human dominant-negative mutation hSK3Δ into the gene coding for the calcium-activated small-conductance potassium channel *KCNN3* ($K_{Ca}2.3$) changed the firing of mice dopamine neurons to a bursting instead of a tonic pattern. Mutant *KCNN3* expression reduced the potassium current and increased the excitability of dopamine by increasing Ca levels, resulting in an elevated accumulation of dopamine and its metabolites. These mice exhibited heightened locomotion and deficits in sensory gating and attention, conditions which could be modeling mania and schizophrenia. Schiemann et al. [74] found that $K_{ir}6.2$ *(Kcnj11)* knockout mice show reduced burst firing in medial substantia nigra dopamine neurons and a deficit in initiating novelty seeking in the open field test, which could be modeling behavior seen during depression. Calcium-dependent homeostatic regulatory mechanisms are essential for regulating the firing pattern of dopamine neurons depending upon sensory stimuli from the environment; any disruption would alter their firing rate [75]. There is substantial evidence that the firing pattern of dopaminergic neurons depends on the proper functioning of calcium and potassium channels. K_v channels play an important role in regulating dopamine release. Martel et al. [76] have shown that studies using specific blockers in rat dorsal striatal brain slices provide evidence that the voltage-gated potassium channels $K_v1.2$, 1.3, and 1.6 play an important role in dopamine release.

It is interesting to speculate that the genetic load of SNPs in voltage-gated ion channels may result in an altered firing pattern of midbrain dopaminergic neurons starting from early development. This would result in altered dopaminergic tone, affecting connections in motivation and reward circuits. We suggest that calcium and potassium channels regulate the excitability of dopamine neurons, and that environmental triggers combined with dysfunctional ion channels might result in an increased dopaminergic tone during mania and a decreased dopaminergic tone during depression in BD patients. This might result in an endophenotype of abnormal motivational reward processing, leading to changes in motivation and risk-taking behaviors; environmental triggers might exaggerate those behaviors seen during mood episodes.

Cognition

BD patients exhibit neurocognitive deficits in multiple domains, including working memory, learning, attention, and executive functioning, both during mood episodes and in the euthymic state [77, 78]. Neurocognitive

assessments of unaffected relatives of BD patients also showed cognitive deficits in verbal learning/memory and in the executive domain of response inhibition [79–81]. Meta-analyses of neurocognitive studies in unaffected relatives of BD patients demonstrated deficits in executive function and verbal memory [82, 83]. Functional imaging studies in bipolar patients have looked for an association of genetic vulnerability to neurocognitive deficits. fMRI of healthy individuals carrying the *CACNA1C* risk variant rs1006737 showed activation deficits in the bilateral hippocampus and anterior cingulate cortex during a cognitive task involving episodic memory recall [84].

The role of calcium and calcium channels in long-term potentiation (LTP) and synaptic plasticity has been well studied. Calcium influx through ion channels plays an important role in activity-dependent gene transcription, enabling organisms to adapt to different stimuli in the environment through synaptic plasticity, learning, and memory. LTCCs, given their location in the neuronal cell body and dendrites, regulate activity-dependent gene expression as they respond to depolarization currents [85, 86]. Ca influx through LTCCs regulates the phosphorylation of cAMP-responsive element-binding protein through the activation of calmodulin kinase (CAMK) and the Ras/mitogen-activated protein kinase (MAPK) signaling cascade [87–89]. The LTCC $Ca_v1.2$ is critical for cellular events during the early development of the hippocampus [90]. LTCCs have been shown to be involved in synaptic plasticity and memory processes in the hippocampus. Mice lacking $Ca_v1.2$ channels in the hippocampus and neocortex show an NMDA-independent loss of protein synthesis, as well as a defect in LTP and synaptic plasticity in the hippocampal region. These mice displayed deficits in learning and spatial memory in response to hippocampus-dependent behavioral tasks [91]. Brain-derived neurotropic factor (BDNF), which plays an important role in synaptic plasticity, is also regulated by LTCCs through the differential activation of BDNF promoters I and III [88, 92–94]. Postsynaptic secretion of BDNF and neurotrophin-3 is also dependent on calcium signaling through L-type calcium channels [95].

Many investigators have observed white matter microstructural abnormalities including hyperintensities in the deep white matter and subcortical gray matter in bipolar patients [96, 97]. An impaired white matter connectivity between frontolimbic circuits and interhemispheric structures has been observed in BD patients [98–100]. Studies have also shown deficits in functional connectivity in the brain of bipolar subjects during cognitive tasks and in the resting state. fMRI of healthy individuals carrying the *CACNA1C* risk variant rs1006737 demonstrated reduced functional coupling between the right and the left hippocampus during a cognitive task [84]. Postmortem brain studies of BD subjects have shown ultrastructural changes in oligodendrocytes, which are precursors of myelination in the CNS; these findings are suggestive of cell death in the prefrontal cortical region and reduced oligodendroglial density in Brodmann area 9 [101, 102]. There is evidence that intact LTCCs are important for oligodendrocyte cell lineage migration, differentiation, maturation, and myelination starting from early stages of development [103–105]. Voltage-gated potassium channels also seem to play an important role in oligodendrocyte maturation and myelination [106]. Dysfunctional ion channel signaling may also result in synaptic plasticity and myelination defects contributing to cognitive deficits, which might be exacerbated during mood episodes.

Stress Response

Patients with BD have trouble regulating their emotions during episodes and also display abnormal stress responses [107]. Small pilot neuroimaging studies have shown amygdala hyperactivation during emotional face reading in youth with BD or at risk of BD; this may potentially be an endophenotype [108]. Resting-state functional connectivity MRI studies using blood oxygenation level-dependent signals have been helpful in identifying connectivity between distinct networks in the brain; one of these studies has demonstrated hyperconnectivity between the right amygdala and the right ventrolateral prefrontal cortex in euthymic BD subjects compared to healthy controls [109]. fMRI of BD subjects carrying the *CACNA1C* risk variant 1006737 displayed a significantly increased activation of the amygdala during a matching task of negative faces (expressing anger and fear) [110]. fMRI of healthy carriers and euthymic BD patients with risk-related variants at either *CACNA1C* rs1006737 or *ANK3* rs10994336 during facial affect processing showed a reduction in connectivity between the visual and the ventral prefrontal cortical regions [111]. LTCCs also play an important role in the consolidation of fearful memories, by modulating LTP in the amygdala [112, 113]. Voltage-gated calcium and potassium channels are also required for the modulation of the firing pattern of gonadotropin-releasing hormone neurons in the hypothalamus [114, 115]. Rhythmic bursts of activity in anterior pituitary neurons are under the influence of voltage-gated calcium channels, and these bursts play a role in the intrinsic regulation of the hypothalamic-pituitary-adrenal axis (HPA) [116]. Altered fear responses and amygdala

activation could well be due to disrupted connections between the prefrontal cortex and the limbic system, especially the amygdala [117]. Expected consequences of such changes might be a decreased ability to process complex tasks involving multiple brain regions. Such tasks might include accurate responses to emotionally charged stimuli, which have been shown to be impaired in BD patients [107, 118].

Genetic variants in voltage-gated ion channels might predispose BD patients to altered stress reactivity due to a dysfunctional HPA axis as well as impaired connectivity between the cortex and the limbic system due to myelination defects; environmental factors might further enhance the reaction to stress leading to further dysfunction.

Circadian Rhythms

Changes in sleep pattern are one of the major triggers for mood episodes in BD patients. Sleep disturbances, including an increased or a decreased need for sleep, an altered sleep/wake cycle, an altered REM onset latency, and difficulty falling asleep are seen not only during mood episodes but also during the euthymic state [119, 120]; such changes are also found in those who are at high risk of developing BD [121]. Increased cholinergic sensitivity and REM density were noticed in remitted bipolar patients in response to the cholinergic drug arecoline [122]. A longer sleep onset latency and an altered REM onset latency are seen in both BD patients and at-risk relatives, and the latter may be the best candidates for an endophenotypic abnormality in the area of sleep [123].

Young subjects who are at high risk of affective disorder as well as euthymic BD patients showed an increased sensitivity to light suppression of melatonin, suggesting that this could be an endophenotype vulnerability marker in those patients [124–126]. Changes in 24-hour temperature and hormonal secretion have been noted in bipolar patients. BD patients have an increased nocturnal temperature and blunted thyroid-stimulating hormone secretion [127, 128]. ClockΔ19 mutant mice show behaviors of increased locomotion, disrupted circadian rhythm, and decreased sensorimotor gating similar to mania [129].

The suprachiasmatic nucleus in the anterior hypothalamus is a major pacemaker that regulates circadian rhythms in the body; this nucleus receives information through the retinohypothalamic tract based on the amount of light stimulating retinal ganglion cells [130–132]. Voltage-gated ion channels can modulate the firing pattern of suprachiasmatic nucleus neurons and retinal photoreceptors, thereby regulating their circadian rhythm. LTCCs also contribute to the depolarization of retinal photoreceptors regulating circadian rhythms through Ras-MAPK-CAMKII and PI3K-Akt signaling [133]. T-type calcium channels play an important role in the transition from high-frequency rhythms to slow oscillations in thalamocortical neurons during the initiation of sleep. Mice with mutations in the gene coding for the alpha 1G unit of the T-type calcium channel show alterations in sleep spindle rhythms in thalamocortical neurons resulting in decreased NREM sleep and increased sleep disturbance [134–137]. Mice that lack the alpha 1B subunit of the N-type calcium channel $Ca_v2.2$ show disturbances in vigilance state with increased consolidation in REM sleep and show an increased interval between NREM sleep and episodes of wakefulness [138].

Variant SNPs in voltage-gated ion channel genes may result in altered circadian rhythms and an altered firing pattern of pacemaker neurons; this might contribute to an endophenotype of delayed sleep onset. This is apart from the environmental trigger-dependent changes due to altered excitability, which may tend to exaggerate the sleep disturbances seen during mood episodes in BD patients.

Energy and Metabolism

Patients with BD experience a change in energy levels, with high energy during elevated mood and low energy during depressive periods, but there is also a subgroup of patients who may experience agitation during depressive episodes. Neurochemical measurements using proton magnetic resonance spectroscopy (MRS) show that ATP metabolite, myo-inositol, and lactate levels are altered in the brain regions of BD patients, indicating an altered energy metabolism and mitochondrial function not only during mood episodes but also in the euthymic state. An MRS study of BD patients demonstrated decreased lactate/Cr levels in both the posterior parieto-occipital and anterior cingulate cortices in the euthymic state [139]. An MRS study of BD subjects showed significantly lower adenosine diphosphate concentrations in the ventrolateral prefrontal cortex of euthymic subjects [140]. A prospective MRS study of offspring of parents with BD found a trend towards increased myo-inositol/Cr concentrations in the dorsolateral prefrontal cortex compared to controls [141]. Another study has shown reduced expression of Na-K-ATPase in response to ethacrynic acid ionic stress challenges in lymphoblastoid cell lines of Old Order Amish BD subjects compared to control subjects within the same Amish pedigree [142]. Goldstein et al. [143] found evidence that SNPs in Na-K-ATPase alpha isoform

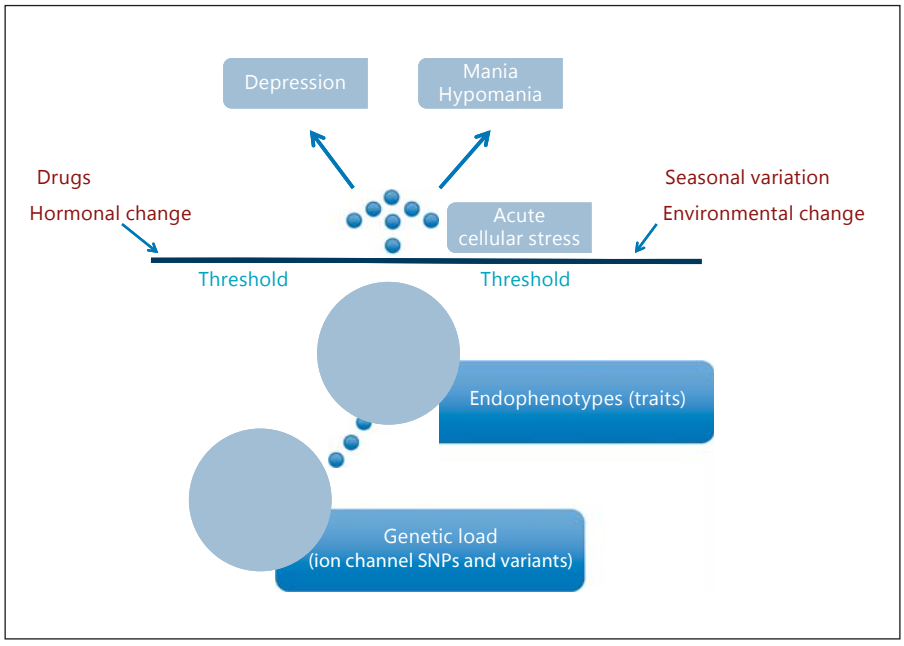

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Fig. 2. Endophenotypes to mood episodes.

genes *(ATP1A1–3)* are significantly associated with BD. The sodium-potassium pump (Na-K-ATPase) controls membrane excitability by exchanging 3 Na ions for 2 K ions by hydrolysis of ATP [144]; dysregulation of Na-K-ATPase would alter the excitability of neurons along with the ATP/adenosine diphosphate balance. Transgenic mice with a mutation in Na-K-ATPase resulting in a reduced efficacy showed increased locomotion as well as reduced anxiety, exploratory behavior, and REM sleep latency behaviors similar to manic patients; cultured cortical neurons from these mutant mice also displayed increased calcium signaling [145]. An imbalance in ATP and myo-inositol shuttling would result in a change in energy production, metabolism, and expenditure. BD patients might have intrinsic deficits in energy production, expenditure, and metabolism due to SNPs in voltage-gated ion channels; these deficits may be further aggravated during mood episodes.

How Are Endophenotypes Associated with a Predisposition to Mood Episodes?

BD patients experience frequent changes in mood, with elevated mood episodes of mania or low mood episodes of major depression. Irritability is also frequently seen in patients with BD, particularly in mixed episodes [146]. Mood episodes do not generally manifest until adolescence or adulthood, although they can be seen in pediatric populations to a lesser extent.

We think that mood episodes are an acute and more magnified manifestation of neurobiological abnormalities underlying endophenotypes under environmental pressure. We propose that environmental triggers such as stress, drugs, seasonal variation, and hormonal and environmental changes, interacting with variants in ion channels, result in altered cellular signaling processes manifesting as mood episodes (fig. 2). Such changes may be mediated by the HPA axis or through the immune system. Treatment of mouse hippocampal slices with corticotropin-releasing hormone seems to alter neuronal excitability depending on L- and T-type calcium channels and also on voltage-gated potassium channels [147]. Antidepressants can alter neuronal excitability by altering calcium and potassium channels, acting as an environmental trigger for mood episodes [148, 149]. Astrocytes from mice treated with the antidepressant fluoxetine (10 mg/kg) for 2 weeks showed an increased expression of the calcium channel protein $Ca_v1.2$ and an increased free cytosolic Ca ion concentration [150]. Seasonal changes can also act as an environmental trigger for mood episodes. Voltage-gated ion channel activity can show diurnal variation in the retina, suprachiasmatic nucleus neurons, and other neural tissues [133]. Immunofluorescence studies of chick cone photoreceptors have found that the expression of LTCCs is under circadian control, with more activation of these channels during the night [151]. Seasonal changes with variation in the amount of darkness and

light during winter and summer may alter ion channel activity; this may be an adaptational advantage in the general population, but it may act as a trigger in BD patients.

Discussion

BD is a syndrome of complex symptoms with characteristic mood episodes of depression and mania or hypomania. In this paper, we have proposed a neurodevelopmental and environmental trigger model for how ion channel abnormalities may contribute to the bipolar phenome. The genetic load of multiple SNPs as well as structural and sequence variants in ion channels would contribute to an altered dopaminergic tone in impulse control and reward processing circuits, synaptic plasticity deficits, an altered HPA axis, myelination defects, circadian rhythm disturbances, and deficits in energy regulation. These developmental deficits alter the neural circuitry, resulting in endophenotypes of abnormal motivational reward processing, white matter hyperintensities, deficits in executive function, altered frontolimbic connectivity, aberrant amygdala activity, melatonin suppression, REM latency, and myo-inositol/ATP shuttling. The endophenotypes are associated with behaviors of poor impulse control, motivational changes, cognitive deficits, abnormal stress response, sleep disturbances, and energy changes. Then, environmental triggers such as stress, drugs, seasonal variation, and environmental and hormonal changes can affect the neurons acutely, altering cellular signaling processes and disturbing the homeostasis between neuronal excitation and inhibition through activity-dependent changes, resulting in full-blown clinical mood episodes (fig. 3). Repeated mood episodes will put the patients at risk of further mood cycling without environmental triggers. These environmental triggers could also modulate gene expression through epigenetic changes beginning in the early developmental phase but expressed phenotypically later in life; this type of environmentally mediated change in gene expression has been described by Lahiri et al. [152] in their LEARn (Latent Early-Life Associated Regulation) model.

The important question of how cycling between different mood states occurs in the same individual needs to be addressed. We propose here that the axon initial segment may be key to mood switching at the neuronal level. The axon initial segment, with a high cluster of sodium, potassium, and calcium channels, regulates the initiation of action potentials and generates electrical patterns in response to environmental input [153]. We think that genetic variations, resulting in structural or regulatory changes in ion channels in the axon initial segmental region, might be the basis for cellular changes that allow the triggering of mood cycling by external or internal stimuli.

The implication of altered ion channels in BD raises several interesting questions. What is the evidence for molecular changes in gene expression and protein levels of ion channel genes implicated in BD, and do these changes occur in key areas, such as in dopaminergic neurons in ventral tegmental area or pacemaker neurons, or in executive control areas, such as the dorsolateral prefrontal cortex? These questions may be addressed at different levels. A microarray gene expression analysis of postmortem prefrontal cortices (Brodmann area 10) from bipolar subjects has shown a differential expression of calcium channel gene *CACNA1A* [154]. A meta-analysis of postmortem brain microarray gene expression studies of BD patients has demonstrated that the potassium channel genes *KCNAB1* and *KCNK1* are differentially regulated in BD [155]. Recently, a gene expression analysis using RNA sequencing from the dorsal prefrontal cortex of bipolar subjects showed that calcium channel genes *(CACNA1C*, *CACNA1E*, *CACNA1G*, *CACNA1H*, *CACNA2D3*, *CACNB1*, *CACNB3*, and *CACNB4)* and potassium channel genes *(KCNA1–4*, *KCNAB1*, *KCNB1*, *KCNB2*, *KCNE3*, *KCNE4*, *KCNH1*, *KCNH2*, *KCNH5*, *KCNH7*, *KCNIP2*, *KCNIP4*, *KCNJ11*, *KCNJ12*, *KCNJ14*, *KCNK1*, *KCNK2*, *KCNK9*, *KCNK12*, *KCNMa1*, *KCNMB2*, *KCNQ2*, *KCNQ3*, *KCNT2*, and *KCNV1)* are differentially expressed in bipolar individuals compared to controls [156]. Gene expression and protein levels in specific neuronal populations in postmortem brains from BD patients have not been studied well, and such studies could give us more specific information at the circuit level. It might be that gene expression, protein level, and modification state (e.g. the phosphorylation state of ion channel regulatory proteins including those that interact with ion channels, structural proteins that hold the ion channels, and cellular signaling proteins that alter the activation state of the ion channels) might play an important role in the pathogenesis of BD.

This paper deals with neurobiological mechanisms underlying ion channel gene variants associated with BD, since there is strong evidence for those genes in BD. However, there are other gene variants that may also play an important role in the pathogenesis of BD [157]. Though the calcium channels have also been associated with BD, schizophrenia, major depression, attention deficit-hyperactivity disorder, and autism as a group, the strongest evidence exists for an association with BD as a single illness [5].

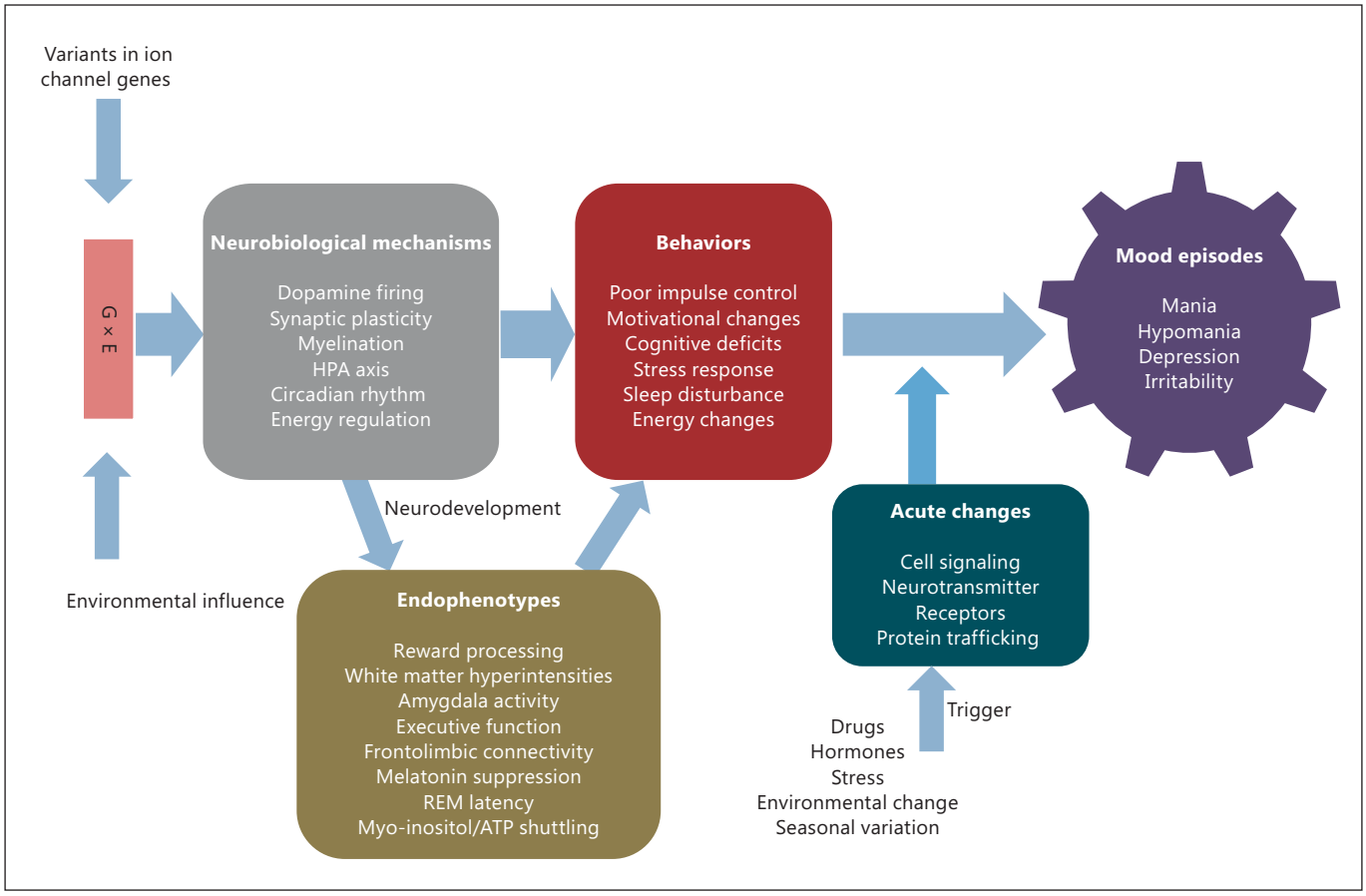

Fig. 3. Bipolar endophenotype-illness model.

Future Directions

BD research is hampered by a lack of appropriate animal models. It might be possible to introduce variants in calcium, *ANK3*, and/or potassium channel genes into a rodent model using genome-editing technologies such as CRISPR [158–160], and one might then study subsequent alterations in neural circuitry. Such studies might further define the nature of BD-related endophenotypes and provide a model in which environmental triggers can reveal symptoms similar to those seen in BD patients during mood episodes. Longitudinal studies in adolescent offspring in high-risk BD families using clinical rating scales, cognitive tasks, functional imaging, and neurochemical studies would be needed to test this model. These studies could potentially result in identifying trait-dependent biomarkers. Understanding the pathophysiology of BD should lead to newer treatment modalities and new mood stabilizers.

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Disclosure Statement

D.K.L. serves on the scientific advisory boards of QR Pharma, Yuma Therapeutics, and Entia BioSciences as well as on the international advisory board of the Drug Discovery and Therapy World Congress; he holds stock options with QR Pharma and a patent involving memantine (the mode of action is not related to that of acamprosate); furthermore, he is Editor in Chief of *Current Alzheimer Research*; finally, he received Research Grant Support from Baxter Healthcare. The authors declare that they have no competing interests.

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