Intracellular Calcium Ion Signaling in Bipolar Mood Disorders: New Data and Directions

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Abstract

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Bipolar mood disorders comprise a heterogeneous group of conditions all of which are characterized by alternations or mixtures of elevated and depressed mood and physiologic arousal. Traditional hypotheses of the neurobiology of bipolar disorder that have invoked increases or decreases in neurotransmitter and receptor activity do not explain the existence at the same time of contradictory emotional states or comorbidity with medical disorders such as hypertension, coronary heart disease and migraine headaches. Unitary changes in neurotransmission also do not elucidate the reason why antidepressant treatments can destabilize the mood disorder, whereas a single medication (mood stabilizer) can ameliorate both poles of this condition. In contrast, changes in basic cellular functions such as the calcium (Ca^{2+}) second messenger system can drive multiple neuronal systems in different directions depending on the sensitivity of a particular system to activation or inhibition by increased concentrations of the second messenger. This article summarizes evidence of elevated baseline and stimulated intracellular calcium ion concentration ($[Ca^{2+}]_i$) in peripheral cells and neuronal cultures in mania and bipolar depression and presents new data on induction of increased lymphocyte $[Ca^{2+}]_{I}$ in a primate separation model. Data are presented supporting calcium antagonist actions of some mood stabilizers and mood stabilizing actions of some calcium channel blockers. This research points to new directions in understanding mood disorders and devising more specific treatments.

1. Introduction

Bipolar disorder is characterized by mixtures and alternations of depressed and pathologically elevated (mania and hypomania) mood. The National Comorbidity Study reported lifetime prevalence rates of bipolar I (history of mania, with or without hypomania), bipolar II (history of hypomania only), and subthreshold (fewer criteria than necessary for formal diagnosis) bipolar disorder in the general population as 1%, 1.1%, and 2.4%, respectively, noting that subsyndromal forms are associated with significant symptomatology and impairment (1). In a structured interview study of patients being treated for depression in two primary care practices, 32.8% of the sample appeared to have subsyndromal bipolar mood disorders, 19% met criteria for bipolar I disorder, and 8.6% had bipolar II disorder (2). Bipolar disorder causes more disability than cancer, epilepsy, and Alzheimer's disease (3). People with bipolar disorder have high rates of suicide, substance use, obesity, heart disease, smoking, and sedentary lifestyle, with consequent increased morbidity and mortality. In 2009, the direct and indirect costs of bipolar I and bipolar II disorder were \$30.7 and \$120.3 billion, respectively (4).

Bipolar disorder is complex psychiatrically and medically. Manic and depressive symptoms may alternate with intervening periods of normal mood (euthymia), or they may cycle frequently; in large numbers of patients, they occur at the same time (5-8). People with bipolar disorder have increased rates of hypertension, hypothyroidism, migraine headaches, and cardiovascular disease. Recurrent affective episodes are associated with loss of brain volume, particularly in the hippocampus. Antidepressants can induce both mania and recurrent depression, but mood stabilizing medications such as lithium can ameliorate and prevent recurrences of both mania and depression.

One recent line of investigation into the pathophysiology that might underlie these complex features has focused on alterations in fundamental cellular mechanisms in systems that regulate mood, thought, behavior and neuroplasticity in bipolar disorder (9). The intracellular calcium ion (Ca^{2+}) is interesting in this regard because it has a biphasic effect in regulating multiple cellular functions. Moderate increases of free intracellular calcium ion concentration $([Ca^{2+}]_i)$ stimulate cellular activity, whereas greater elevations inhibit the same functions and even higher levels within the physiologic range induce cellular apoptosis (10). Alterations of intracellular Ca^{2+} signaling in excitatory and inhibitory systems could change the balance between these systems, leading to alternations between mania and depression (11), while depression and could occur mania simultaneously if a hyperactive intracellular Ca^{2+} signal produced behavioral and emotional activation in some systems and suppression in others. Enhancement of Ca²⁺ signaling by antidepressants could lead to antidepressant-induced mania. while of attenuation increased intracellular calcium signaling could explain why mood stabilizers can improve both mania and bipolar depression. Increased intracellular calcium signaling can induce oxidative stress and apoptosis, contributing to the neuronal loss that has been observed with recurrent manic and depressive episodes (9). Hyperactive calcium signaling in other organs could play a role in the comorbidity of bipolar mood disorders with other

conditions linked to hyperactive intracellular calcium signaling such as migraine headaches, hypertension and cardiovascular disease.

2. Intracellular calcium ion signaling

Within neurons, intracellular Ca²⁺ signaling regulates excitability, brain rhythms, the sleep-wake cycle, information processing, perception, sensory cognition, neurotransmission, synaptic proteins. regulation of expression of multiple genes, consciousness, remodeling of neuronal architecture, and synaptic plasticity (11). Neuroplasticity, which depends on intracellular signaling, is the capacity of the central nervous system to develop and sustain adaptive responses to internal and external stimuli, resulting among other things in neuronal resilience and mood stabilization (9).

2.1 Regulation of intracellular calcium ion signaling

Free intracellular Ca²⁺ concentration $([Ca^{2+}]_i)$ is normally regulated tightly at approximately 100 nM, or 0.0001 of the Ca^{2+} concentration in the extracellular fluid. Most intracellular calcium is stored in organelles such as mitochondria and the endoplastic reticulum, or is complexed with binding proteins (12). Free intracellular calcium levels are increased rapidly by release from intracellular stores; influx through calcium channels replenishes intracellular stores and helps to regulate the baseline level of intracellular Ca^{2+} ([Ca^{2+}]_B), which in turn influences neuronal excitability. Cellular activation, for example

by agonists such as neurotransmitters, increases $[Ca^{2+}]_i$ to stimulated levels $([Ca^{2+}]_S)$, which are then returned to baseline by active transport of Ca^{2+} into intracellular stores and out of the cell.

Agonist interactions with G-protein coupled receptors activates turnover of the membrane phosphatidylinositol (PI) system, beginning with hydrolysis of membranebound phosphatidylinositol biphosphate (PIP2) and ultimately producing two metabolismproducts inositol of triphosphate (IP₃) and diacylglycerol (DG). IP₃ acts on mitochondrial and other intracellular receptors to promote release of stored Ca^{2+} , while DG attracts the intracellular enzyme PKC to the cell membrane, where it is activated by free intracellular Ca²⁺ in order to phosphorylate intracellular proteins that regulate cellular processes. IP₃ and DG are then combined to reconstitute PIP2 through a number of steps for another round of cellular activation.

2.2 Calcium channels

Calcium ions enter the cytosol from the extracellular space through receptoroperated channels gated by receptors for hormones and neurotransmitters, such as some catecholamines and the excitatory acids. potential amino and through dependent channels (PDCs or voltage-gated channels), which are gated by membrane potential (13). In the brain, potentialdependent calcium channels are localized in regions rich in synapses, perhaps because high [Ca²⁺], must be produced rapidly to regulate neurotransmitter release. Additional pathways for calcium entry include leakage through an ungated channel and exchange of

extracellular calcium ions for intracellular sodium ions (Na^+) . Under physiological conditions, PDCs can be regulated by receptor-mediated events, such as the production of inositol triphosphate, and receptor-operated channels can be gated by changes in membrane potential. Endogenous regulators, which may be altered in disease states, appear to modulate PDC gating. Furthermore, extracellular Ca²⁺ entering the cell may release calcium ions from intracellular stores, and trigger amounts of calcium ions released from intracellular stores may facilitate calcium channel opening. Even subtle alterations of the function of one kind of calcium channel can therefore have significant effects on the overall balance of calcium-dependent cellular activity.

The PDC consists of a central pore-forming CaV subunit and five allosterically linked units called α_1 , α_2 , β , γ , and δ (14). There are 10 CaV-a1 subunits organized into various calcium channels. The mammalian nervous system contains 9 of the 10 major calcium channel types, with even more functional diversity related to alternative splicing events, as well as association with different subunits and regulatory proteins (15). Thus far, four separate genes coding for the α_1 subunit have been identified. The $\alpha 1C$ subunit of the CaV1.2 channel, a primary source of Ca²⁺ entry for plasma membrane to nucleus signaling in the brain, is coded by the CACNA1C gene, an allele of which has been associated with bipolar disorder (11). The other subunits, and possibly other endogenous circulating factors, can alter the conformation of the α_1 subunit, changing the activity of the calcium channel and its affinity for medications that bind to it.

Different calcium channels in the nervous system perform different physiologic functions, and multiple copies of the same channel interact to fine tune cellular regulation (15). The L (for long-lasting) channel requires significant depolarization for Ca^{2+} entry and inactivates slowly. Of the four members of the L-type channel family (CaV1.1-1.4), only CaV1.2 and CaV1.3 play a prominent role in the brain, the former in the hippocampus and the latter in the limbic system and striatum (16). L-type calcium channels (LTCCs) do not participate directly in neurotransmitter release, but they play an important role in setting overall neuronal excitability: CaV1.2-based channels influence gene transcription and gene expression (11).

The T (transient) channel is activated by depolarizations small and inactivates rapidly. T-type calcium channels may be involved in the action of the anticonvulsants ethosuximide, valproic acid and divalproex in the treatment of absence seizures. The N (neither L nor T) channel, which is primarily found on central nervous system (CNS) neurons, as are rapidly inactivating P (Purkinje cell) channels in cerebellar Purkinje cells, Q channels, and R (resistant to calcium channel blocker) channels, all participate in neurotransmitter release.

3. Ca²⁺ signaling in bipolar disorder

The study of intracellular Ca²⁺ dynamics in bipolar disorder initially involved blood platelets as a proxy for brain neurons because of their similar function and common embryonic origin (10). Platelet activators such as thrombin, platelet activating factor (PAF) and serotonin, act through G-proteins to activate membrane

PIP₂ breakdown and generate IP₃ and DG; IP₃ interacts with IP₃ receptors to release Ca^{2+} from stores in the endoplasmic reticulum (ER) and mitochondria, which then activates calcium influx to restore stores (12). Thapsigargin, which inhibits ER calcium-ATPase, causes Ca^{2+} release from the ER (12).

Compared with controls, elevations have been found in bipolar disorder in resting free intracellular calcium ion concentration $([Ca^{2+}]_B)$, as well as the rise in intracellular calcium ion concentration ($[Ca^{2+}]_s$) stimulated by agonists such as thrombin, PAF. serotonin, dopamine. fonnylrnethionylleucylphenylalanine, and various mitogens, in blood platelets, lymphocytes, B-lymphoblast cell lines (BLCLs), olfactory neurons, and neuroblastoma cells (17-24). Most studies have reported similar elevations in mania and bipolar depression, which normalize with normalization of mood after treatment with various medications or electroconvulsive therapy (ECT) (20).Similar findings with different agonists in different cells from patients with bipolar disorder, along with the finding of lack of increase of $[Ca^{2+}]_i$ in control platelets after incubation with a plasma ultrafiltrate from bipolar disorder patients with elevated $([Ca^{2+}]_i)$ platelet (25), suggest that hyperactive intracellular Ca²⁺ signaling represents a generalized primary change in intracellular calcium ion dynamics rather than the result of a circulating substance such as cortisol that might be elevated in bipolar disorder.

Most studies find increased $[Ca^{2+}]_B$ and agonist-induced $[Ca^{2+}]_s$ in mania and bipolar depression, but not unipolar depression (22, 26, 27). However, platelet $[Ca^{2+}]_s$ in

response to serotonin was increased in major depressive disorder compared with controls, the increase being significantly greater in depressed patients with high anxiety than in those with low anxiety (28). Stimulation of olfactory receptor neurons from medication free euthymic bipolar disorder patients, 10 euthymic bipolar patients treated with mood stabilizers, and 17 controls, with odorants, which increase IP₃ levels, resulted in lower $[Ca^{2+}]_{s}$ in euthymic medicated patients than controls (28.8 vs 86 nM) (18). The unusually low baseline levels of $[Ca^{2+}]_i$, small N, and use of euthymic patients prevent comparisons with other studies.

To examine whether changes in $[Ca^{2+}]_i$ are inducible by the kinds of experiences associated with mood disorders, lymphocyte $[Ca^{2+}]_i$ was measured in infant pigtail and bonnet macaque monkeys separated from their mothers or peers during studies of stress-induced immune suppression, which produces observable agitation, distress and depression that remits with reunion (29-32). There were no differences in lymphocyte [Ca²⁺]_i between animals prior to separation and after reunion with the mother or peer group. However, during separation, mean $(\pm SEM)$ [Ca²⁺]_B (Figure 1) increased from 81.73 ± 2.51 nM to 139.8 ± 10.78 nM (paired t-test t=5.771, df=10, p=0.0002). Mean mitogen-stimulated $[Ca^{2+}]_s$ (Figure 2) increased from 198.5 \pm 20.81 nM to 334.2 \pm 36.58 nM (paired t test t=3.282, df=10, p=0.0083). Both measures of $[Ca^{2+}]_i$ returned to pre-separation values with reunion (Dubovsky SL, Laudenslager ML, Reite ML: previously unpublished data). These results imply that loss, a precipitating stress clearly implicated in mood disorders, reversible cause alterations can in intracellular Ca²⁺ signaling that could alter affective and behavioral regulation and induce immune suppression.

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Figure 1



Figure 2

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3.1 Calcium channels and intracellular stores in the regulation of $[Ca^{2+}]_i$ in bipolar disorder

A polymorphism of the CACNA1C gene, which encodes the α 1C subunit of the L-type calcium channel CaV1.2, has been linked to bipolar disorder (11, 15, 16, 33-36), as well as to associated alterations in intracellular calcium ion homeostasis (37) and circadian rhythms (36). This channel plays a central role in regulating gene transcription and the tonic excitatory drive (11), raising the suggestion that bipolar disorder could represent a channelopathy, similar to familial migraine and some seizure disorders (38). As already noted, L-type calcium channel dysfunction could contribute to elevated $[Ca^{2+}]_B$ and resting neuronal excitability, as well as to replenishing of intracellular Ca^{2+} stores.

The immediate source of elevated $[Ca^{2+}]_i$ with neuronal activation in bipolar disorder appears to involve increased release from intracellular calcium stores promoted by inositol triphosphate (IP₃) (39, 40). Support this possibility is provided by for observations that thapsagargin, which promotes release of stored intracellular Ca^{2+} , increases platelet and lymphocyte $[Ca^{2+}]_i$ in bipolar disorder (12). Along these lines, IMPA2, the gene for inositol monophosphatase, the rate limiting step in reconstitution of membrane PIP₂, is thought to be a susceptibility gene for bipolar disorder (9). Mitochondria play an essential role in regulation of intracellular Ca^{2+} . particularly in platelets, and mitochondrial dysfunction has been reported in parallel with intracellular Ca^{2+} dysregulation in bipolar disorder (12, 41).

One possible mediator of increased release of stored intracellular calcium is amplified production of IP₃ as a result of increased PI turnover that is either primary or secondary hyperactive G-protein. a Another to potential mechanism that has been a subject of recent research involves neuronal calcium sensor-1 (NCS-1), a calcium binding protein expressed in neurons that enhances the response of the IP_3 receptor to IP_3 in both a calcium-dependent and calcium-independent manner (42). Both over-expression (43) and under-expression (44) of NCS-1 have been noted in bipolar disorder.

Another line of investigation into the mechanism of increased release of Ca²⁺ from intracellular stores in bipolar disorder involves B-cell lymphoma-2 (Bcl-2), an antiapoptic and pro-neurotrophic protein located on the ER and outer mitochondrial membrane that interacts with the IP_3 receptor to inhibit release of stored Ca^{2+} (9, 40). Decreased Bcl-2 activity, which has been reported in bipolar disorder, may contribute to increased Ca^{2+} release from intracellular stores in bipolar disorder (9, 40). Both loss of the anti-apoptotic function and increased $[Ca^{2+}]_i$ could promote loss of cerebral grey matter in some bipolar disorder patients (40). In lymphoblasts of patients with bipolar disorder, those with an SNP of the Bcl-2 gene associated with decreased gene expression have been found to have increased $[Ca^{2+}]_B$, as well as increased IP₃-mediated [Ca²⁺]_s, presumably associated with greater release from intracellular stores (11, 40, 45). Lithium (9, 40), valproate (11), and ECT (9), all of which are effective treatments for bipolar disorder, have been noted to up-regulate Bcl-2 gene expression, in some studies in conjunction with reducing elevated $[Ca^{2+}]_i$ in platelets of patients with bipolar disorder (9, 40).

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4. Calcium antagonist actions of mood stabilizing medications

Lithium, the prototypical mood stabilizing medication that is effective for both poles of bipolar mood disorders, reduces elevated $[Ca^{2+}]_B$ and $[Ca^{2+}]_S$ in peripheral cells of patients with bipolar disorder but does not affect normal $[Ca^{2+}]_i$ in most studies (46). One hypothesized mechanism of attenuation of hyperactive intracellular calcium signaling is that lithium inhibits inositol monophosphatase, the rate limiting step in reconstitution of PIP2 which, as noted earlier, is up-regulated in some cases of bipolar disorder; inhibition of the enzyme would eventually deplete IP₃, decreasing Ca^{2+} intracellular release both and

production of PKC (9). Another pertinent action of lithium is inhibition of thrombin stimulated calcium flux through the transient receptor potential canonical type 3 (TRPC3) channel in human astroglioma cells (47). In B-lymphoblast cell lines from bipolar I patients, lithium attenuated lysophosphatidic acid (LPA) (agonist)- but not thapsigargin (TG)- induced (store depletion) induced mobilization of intracellular Ca^{2+} . suggesting that lithium did not directly alter release of Ca^{2+} from intracellular stores (48). In contrast, lithium inhibits the action of NCS-1 on the IP₃ receptor, which would be expected to interfere with Ca^{2+} release from intracellular stores (42). Mechanisms of calcium antagonism by lithium that could be relevant to reduction of $[Ca^{2+}]_i$ are summarized in Table 1 (9, 16, 17, 21, 27, 42, 47-49).

Table 1.Calcium Antagonist Actions of Lithium

- Reduced Ca2+ release from intracellular stores resulting from competitive inhibition of inositol-1-monophosphatase
 - Reduced production of inositol triphosphate (IP₃)
 - Competitive inhibition results in increased inhibition with increased PI turnover
- Inhibition of the calcium binding protein neuronal calcium sensor-1 (NCS-1)
 - \circ NCS-1 promotes release of Ca2+ from intracellular stores by enhancing responsiveness of IP₃ receptors
- Reduction of calcium influx that replenishes intracellular stores
- Down-regulation of metabotropic glutamate receptors
- Enhancement of calcium efflux through an effect on sodium countertransport
- Antagonism of a hyperactive G protein by competition for magnesium ion binding required for G protein dissociation
- Induction of Bcl-2
- Inhibition of glycogen synthase kinase-3β
 - Enhances membrane stability
 - Inhibition of protein kinase C (PKC)

Carbamazepine, which has been in use as a mood stabilizer since 1962 (50), inhibits Ca^{2+} currents in a variety of cellular models (51), and the time course of suppression of

calcium-dependent potentials is comparable to that produced by the calcium channel blocker verapamil (52). In vitro incubation with carbamazepine significantly lowers

lymphocyte $[Ca^{2+}]_i$ in ill bipolar patients but not in controls or euthymic bipolar disorder Valproate. patients (46). another anticonvulsant with mood stabilizing and especially antimanic properties (53), was found to reduce lysophosphatidic acid (LPA)-stimulated increased $[Ca^{2+}]_i$ in B lymphoblast cell lines from bipolar disorder patients to an extent similar to lithium, as well as thapsagargin-stimulated release of Ca^{2+} from intracellular stores (48). A study of transmitochondrial hybrid cells suggested that valproate may reduce elevated $[Ca^{2+}]_i$ only in cells with elevated mitochondrial levels calcium (54). Incubation of astrocytoma cells for 48 hours with therapeutic concentrations of valproate inhibited muscarinic receptor-stimulated increased $[Ca^{2+}]_i$ while slightly decreasing PKC activity (55).

Lamotrigine, another anticonvulsant that may be useful in some cases of bipolar disorder but is not as effective for mania as for depression (56), also has calcium channel blocking properties (57). Unlike lithium and valproate, lamotrigine did not (LPA)reduce lysophosphatidic acid stimulated increased $[Ca^{2+}]_i$ or thapsagargin stimulated release of Ca²⁺ from intracellular stores in B lymphoblast cell lines from bipolar disorder patients (48). Interestingly, levetiracetam, an N-type calcium channel antagonist anticonvulsant that does not appear to have reliable mood stabilizing properties (58), does not alter increased $[Ca^{2+}]_i$ in platelets of bipolar disorder patients (21). ECT, the most effective treatment for both mania and depression, decreases IP₃ receptor expression in rat brain (16), but $[Ca^{2+}]_i$ before and after ECT has not been studied.

5. Calcium channel blockers as mood stabilizers

Calcium antagonist actions of established mood stabilizing medications tend to support an important role of calcium signaling in bipolar disorder, but such actions could be unrelated to the primary mood stabilizing effect. Further evidence in favor of a role of intracellular Ca²⁺ could be provided by antimanic or mood stabilizing actions of medications the primary action of which is to attenuate increases in $[Ca^{2+}]_{i}$. The calcium channel blockers (CCBs), which reduce Ca^{2+} influx from the extracellular space, are candidates in this regard, in that reduction of tonic calcium influx may decrease baseline neuronal excitability and reduce replenishment of the intracellular pool from which more immediate release results in rapid neuronal activation (59).

There are 10 calcium channel blockers (CCBs) currently approved by the FDA, belonging to four chemical classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), dihydropyridines or DHPs (nifedipine, amlodipine, felodipine, isradipine, nicardipine, nisoldipine, and nimodipine), and diarylaminopropylamines (bepridil) (16, 35, 60). All CCBs inhibit calcium influx through potential dependent calcium channels via activity-dependent binding to the α 1 subunit of LTCCs. In addition to binding to L-channels, nimodipine, nicardipine, methoxyverapamil, flunarizine, and cinnarizine may also antagonize Tchannels, and a phenlyalkylamine binding site exists on the inner mitochondrial membrane Because (16). of their heterogeneity of structure, binding site, and medications are action. these not

interchangeable. However, they all have the capacity to reduce excessive excitability of diverse cellular systems. CCB binding to Lchannels is enhanced by depolarization and reduced by hyperpolarization (14), resulting in greater activity in hyperactive tissue. While CCBs are primarily used to treat cardiovascular disorders, verapamil and norverapamil can be recovered from human cerebrospinal fluid (CSF) after oral administration (61), and the concentration of phenylalkylamines and other CCBs in the brain is sufficient to be protective after cerebral ischemia in animal models (62, 63). The lipophilic nimodipine crosses the blood-brain barrier readily and is approved for the treatment of stroke.

5.1. Studies of CCBs in bipolar disorder

Following double blind, placeboa controlled trial of verapamil in a single manic patient (64), case reports appeared of prevention by verapamil of antidepressantinduced hypomania (65, 66), and prevention of affective recurrence in bipolar disorder (67). Open trials of verapamil were effective in 4 of 7 manic patients (68), and in all patients with mania, 3/4 of patients with mixed episodes, and about 1/3 of acutely depressed patients in a sample of 28 women (69). Formal studies of CCBs have generally been small and relatively brief, with an emphasis on acute treatment of mania. For example, double-blind protocols, in verapamil was superior to placebo in six manic patients (70) and 7 manic or schizoaffective-manic patients (71). Doubleblind comparisons reported equivalent antimanic efficacy to lithium (72-75) and clonidine (76). In open trials, addition of verapamil (77, 78) or diltiazem (79, 80) improved the response to lithium in primary mania, but not mania secondary to central

nervous system disease (80). In trials with varying levels of blinding, nimodipine was found to be effective for complex and refractory bipolar disorder, both alone (81-86) and in combination with lithium (87) or carbamazepine (83), including in some patients with neurological disorders. A retrospective analysis of open administration diltiazem suggested benefit in treatmentresistant bipolar disorder (79), and a singleblind trial suggested benefit of isradipine for bipolar depression (35), but no further research has been reported on either drug. Two negative trials of verapamil in mania (88, 89) had larger sample sizes, but they were limited by brief treatment and use of doses that were lower than doses that have been found effective in other experience.

6. Conclusions

Traditional neurobiological hypotheses that emphasize altered neurotransmitter and receptor function have failed to explain the rapidly changing alternations and mixtures of depressed and elevated mood in conditions like bipolar disorder, and they do not predict response to particular treatments or explain why the same treatment can be effective for both mania and bipolar depression. Another limitation of these hypotheses is that they do not explain common medical comorbidities of mood disorders such as hypertension, coronary heart disease, and migraine headaches.

Newer lines of investigation addresses fundamental changes in cellular activity that impact multiple downstream functions. In particular, intracellular Ca^{2+} has a biphasic effect on cellular activities, with the potential to produce contradictory changes

at different concentrations in different locations. Such universal intracellular signals have a potential impact on organ systems throughout the body and have been linked to the pathophysiology of associated medical conditions that involve cellular hyperactivity. It remains to be determined whether increased $[Ca^{2+}]_i$ is a downstream effector arm of a primary change in cellular function, or whether it is an intermediate step in a cascade of changes. A number of issues amplify widely replicated findings of increased intracellular Ca²⁺ signaling in a variety of peripheral cells and some preparations neuronal and possible mechanisms of elevated $[Ca^{2+}]_i$.

One issue is that both the mean and interindividual variability of $[Ca^{2+}]_i$ are increased in bipolar disorder (20). Standard deviations of $[Ca^{2+}]_B$ and $[Ca^{2+}]_S$ are significantly greater in bipolar disorder than in controls, and both decrease to the control range with normalization of mood (20, 90). Variability in $[Ca^{2+}]_i$ parallels the heterogeneity of bipolar (and most psychiatric) disorders (91). Cases of bipolar disorder vary in features such as specific symptoms, severity, depression. presence psychosis, of comorbidity, intrusion of the mood disorder into the personality, traumatic experiences, course, family history, and treatment response. It seems likely that some bipolar phenotypes involve changes in intracellular Ca^{2+} signaling, while others may be related to a different pathophysiology. Studies correlating specific clinical features with specific biological findings would help to elucidate whether there is a particular constellation of features correlated with altered $[Ca^{2+}]_i$.

No established treatment is universally effective. Any given treatment will be

effective for some patients and not others. Thus far, there are no consensual markers to guide treatment choice. It would therefore be useful to study whether elevated $[Ca^{2+}]_i$ preferential response predicts а to established mood stabilizers with prominent calcium antagonist properties such as lithium or possibly to CCBs. This question could be addressed with prospective followup of a sufficient number of patients with and without this finding. Since the heterogeneity of CCB binding sites provides for different spectra of action of different CCBs, another informative line of research would be to determine whether binding of a particular medication to calcium channels that are more localized to the central nervous system (e.g., dihydropyridine CCBs that act on T- as well as L-type channels (86)) would predict a response to that medication. Studies of CCBs might be supplemented by studies of medications that act on mediators of intracellular Ca²⁺ signaling such as tamoxifen, an estrogen receptor antagonist that inhibits protein kinase C and had acute antimanic properties in a small controlled trial (92). Absence of reliable sources of funding for such research makes it challenge to conduct systematic clinical trials of sufficient size.

Measuring $[Ca^{2+}]_i$ with intracellular calcium chelating dves is tedious and time consuming. Lack of established reference ranges requires measuring $[Ca^{2+}]_i$ in controls contemporaneously with patients, generally at the same time of day and year to minimize the potential impact of circadian and seasonal changes. Given the technical challenges and expense in measuring $[Ca^{2+}]_i$ in peripheral cells, such measures are not likely to prove practical in the clinic, even if further research clarifies some of the questions raised here. From a scientific standpoint. however, this research

exemplifies a conceptual shift away from neurotransmitters and receptors to more fundamental elements of cellular function. A parallel change in direction has involved a shift in focus from specific regions of the brain to neuronal networks that integrate information from multiple locations (93). These lines of investigation help us to learn more about ways in which dysfunction of

intracellular systems in the brain and the body assort to produce constellations of features that may be addressed more efficiently by directing treatments at measurable cellular derangements rather than diagnoses that are not yet specific enough to direct us to inform specific choice of therapy.

References

1. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64:543-52.

2. Dubovsky SL, Leonard K, Griswold K, daurignac E, Hewitt B, Fox C, et al. Bipolar disorder is common in depressed primary care patients. Postgraduate Medicine. 2011;123:129-33.

3. Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Arch Gen Psychiatry. 2011;68:241-51.

4. Dilsaver SC. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. J Affective Disord. 2011;129:79-83.

5. Suppes T, Mintz J, McElroy SL, Altshuler LL, Kupka R, Frye MA, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. Arch Gen Psychiatry. 2005;62:1089-96.

6. Vazquez GH, Lolich M, Cabrera C, Jokic R, Kolar D, Tondo L, et al. Mixed symptoms in major depressive and bipolar disorders: A systematic review. J Affective Disord. 2018;225:756-60.

7. Sajatovic M, Jurdi R, Gildengers A, Greenberg RL, Tenhave T, Bruce ML, et al. Depression symptom ratings in geriatric patients with bipolar mania. Int J Geriatric Psychiatry. 2011;26:1201-8.

8. Dubovsky SL, Dubovsky AN. Concise Guide to Mood Disorders. Washington, D. C.: American Psychiatric Press; 2002. 9. Soeiro-de-Souza MG, Dias VV, Figueira ML, Forlenza OV, Gattaz WF, Zarate CA, et al. Translating neurotrophic and cellular plascticity: from pathophysiology to improved therapeutics for bipolar disorder. Acta Psychiatrica Scandinavica. 2012;126:332-41.

10. Dubovsky SL, Franks RD. Intracellular calcium ions in affective disorders: a review and an hypothesis. Biol Psychiatry. 1983;18:781-97.

11. Berridge MJ. Calcium signalling and psychiatric disease: bipolar disorder and schizophrenia. Cell Tissue Res. 2014;357:477-92.

12. Kato T. Role of mitochondrial DNA in calcium signaling abnormality in bipolar disorder. Cell Calcium. 2008;44:92-102.

13. Dubovsky SL. Calcium channel inhibitors. In: Sadock BJ, Sadock VA, Ruiz P, editors. Comprehensive Textbook of Psychiatry. 2. 10 ed. Baltimore: Lippincott Williams & Wilkins; 2017. p. 3015-22.

14. Berger SM, Bartsch D. The role of L-type voltage-gated calcium channels Cav1.2 and Cav1.3 in normal and pathological brain function. Cell & Tissue Research. 2014;357:463-76.

15. Zamponi GW. Targeting voltagegated calcium channels in neurological and psychiatric diseases. Nature Reviews Drug Discovery. 2016;15:19-34.

16. Casamassima F, Hay A, Benedetti A, Lattanzi L, Cassano GB, Perlis RH. L-type calcium channels and psychiatric disorders: a brief review. Am J Med Genet Part B. 2010;153B:1373-90.

17. van Calker D, Forstner U, Bohus M, Gebicke-Harter P, Hecht H, Wark H-J, et al. Increased sensitivity to agonist stimulation of the Ca2+ response in neutrophils of manic-depressive patients: effect of lithium

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therapy. Neuropsychobiology. 1993;27:180-3.

18. Hahn CG, Gomez G, Restrepo D, Friedman E, Josiassen R, Pribitkin EA, et al. Aberrant intracellular calcium signaling in olfactory neurons from patients with bipolar disorder. Am J Psychiatry. 2005;162:616-8.

19. Kato T. Molecular neurobiology of bipolar disorder: a disease of "mood-stabilizing neurons"? Trends in Neuroscience. 2008;31:495-503.

20. Dubovsky SL, Christiano J, Daniell LC. Increased platelet intracellular calcium concentration in patients with bipolar affective disorders. ArchGenPsychiatry. 1989;46:632-8.

21. Dubovsky SL, Daurignac E, Leonard KE, Serotte JC. Levetiracetam, calcium antagonism, and bipolar disorder. J Clin Psychopharmacology. 2015;35:422-7.

22. Dubovsky SL, Lee C, Christiano J. Elevated intracellular calcium ion concentration in bipolar depression. BiolPsychiatry. 1991;29:441-50.

23. Dubovsky SL, Murphy J, Thomas M, Rademacher J. Abnormal intracellular calcium ion concentration in platelets and lymphocytes of bipolar patients. Am J Psychiatry. 1992;149(1):118-20.

24. Dubovsky SL, Murphy.J, Christiano J, Lee C. The calcium second messenger system in bipolar disorders: data supporting new research directions. Journal of Neuropsychiatry and Clinical Neurosciences. 1992;4:3-14.

25. Dubovsky SL, Thomas M, Hijazi A, Murphy J. Intracellular calcium signalling in peripheral cells of patients with bipolar affective disorder. EurArchPsychiatry Clin Neurosci. 1994;243:229-34.

26. Dubovsky SL, Murphy J, Thomas M, Rademacher J. Abnormal intracellular calcium ion concentration in platelets and lymphocytes of bipolar patients. AmJPsychiatry. 1992;149:118-20.

27. Dubovsky SL, Thomas M, Hijazi A, Murphy J. Intracellular calcium signalling in peripheral cells of patients with bipolar affective disorder. Eur Arch Psychiatry Clin Neurosci. 1994;243(5):229-34.

28. Delisi SM, Konopka LM, O'Connor FL, Crayton JW. Platelet cytosolic calcium responses to serotonin in depressed patients and controls: relationship to symptomatology and medication. Biol Psychiatry. 1998;43:327-34.

29. Boccia ML, Reite ML, Kaemingk K, Held P, Laudenslager ML. Behavioral and autonomic responses to peer separation in pigtail macaque monkey infants. Developmental Psychobiology. 1989;22:447-61.

30. Laudenslager ML, Berger CL, Boccia ML, Reite ML. Natural cytotoxicity toward K562 cells by macaque lymphocytes from infancy through puberty: effects of early social challenge. Brain, Behavior, & Immunity. 1996;10:275-87.

31. Laudenslager ML, Boccia ML, Berger CL, Gennaro-Ruggles MM, McFerran B, Reite ML. Total cortisol, free cortisol, and growth hormone associated with brief social separation experiences in young macaques. Developmental Psychobiology. 1995;28:199-211.

32. Laudenslager ML, Reite ML, Harbeck RJ. Suppressed immune response in infant monkeys associated with maternal separation. Behavioral & Neural Biology. 1982;36:40-8.

33. Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, et al. Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. Hypertension. 2016;68:1132-8.

34. Casamassima F, Huang J, Fava M, Sachs GS, Smoller JW, Cassano GB, et al. Phenotypic effects of a bipolar liability gene among individuals with major depressive disorder. Am J Med Genet Part B. 2010;153B:303-9.

35. Ostacher M, Iosifescu DV, Hay A, Blumenthal SR, Sklar P, Perlis RH. Pilot investigation of isradipine in the treatment of bipolar depression motivated by genomewide association. Bipolar Disorders. 2014;16:199-203.

36. McCarthy MJ, Le Roux MJ, Wei H, Beesley S, Kelsoe JR, Welsh DK. Calcium channel genes associated with bipolar disorder modulate lithium's amplification of circadian rhythms. Neuropharmacology. 2016;101:439-48.

37. Uemura T, Green M, Warsh JJ. CACNA1C SNP rs1006737 associates with bipolar I disorder independent of the Bcl-2 SNP rs956572 variant and it associated effect on intracellular calcium homeostasis. World Journal of Biological Psychiatry. 2016;17:525-34.

38. Keers R, Farmer AE, Aitchison KJ. Extracting a needle from a haystack: reanalysis of whole genome data reveals a readily translatable finding. Psychological Medicine. 2009;39:1231-5.

39. Hough C, Lu S-J, Davis CL, Chuang D-M, Post RM. Elevated basal and thapsigargin-stimulated intracellular calcium of platelets and lymphocytes from bipolar affective disorder patients measured by a fluorometric microassay. Biol Psychiatry. 1999;46:247-55.

Machado-Vieira R, Pivovarova NB, 40. Stanika RI, Yuan P, Wang Y, Zhou R, et al. Bcl-2 polymorphism The gene rs9565722AA inositol 1,4,5increases trisphosphate receptor-mediated endoplasmic reticulum calcium release in subjects with disorder. Biol bipolar Psychiatry. 2011;69:344-52.

41. Kato T. Neurobiological basis of bipolar disorder: Mitochondrial dysfunction hypothesis and beyond. Schizophrenia Res. 2017;187:62-6.

42. Schlecker C, Boehmerle W, Jeromin A, DeGray B, Varshney A, Sharma Y, et al. Neuronal calcium sensor-1 enhancement of InsP3 receptor activity is inhibited by therapeutic levels of lithium. J Clin Invest. 2006;116:1668-74.

43. Koh PO, Undle AS, Kabbani N, Levenson R, Goldman-Rakic PS, Lidow MS. Up-regulation of neuronal calcium sensor-1 (NCS-1) in the prefrontal cortex of schizophrenic and bipolar patients. PNAS. 2003;100(1):313-7.

44. Torres KC, Souza BR, Miranda DM, Sampaio AM, Nicolato R, Neves FS, et al. Expression of neuronal calcium sensor-1 (NCS-1) is decreased in leukocytes of schizophrenia and bipolar disorder patients. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2009;33:229-34.

45. Uemura T, Green M, Corson TW, Perova T, Li PP, Warsh JJ. Bcl-2 SNP rs956572 associates with disrupted intracellular calcium homeostasis in bipolar I disorder. Bipolar Disorders. 2011;13:41-51.

46. Dubovsky SL, Lee C, Christiano J. Lithium decreases platelet intracellular calcium ion concentrations in bipolar patients. Lithium. 1991;2:167-74.

47. Uemura T, Green M, Warsh JJ. Chronic LiCl pretreatment suppresses thrombin-stimulated intracellular calcium mobilization through TRPC3 in astroglioma cells. Bipolar Disorders. 2016;18:549-62.

48. Perova T, Kwan M, Li PP, Warsh JJ. Differential modulation of intracellular Ca2+ responses in B lymphoblasts by mood stabilizers. International Journal of Neuropsychopharmacology. 2010;13:693-702.

49. Valvassori SS, Dal-Pont GC, Resende WR, Varela RB, Peterle BR, Gava FF, et al. Lithium and tomoxifen modulate behavior and protein kinase C activity in the animal model of mania induced by ouabain. Int J Neuropsychopharmacol. 2017;20(11):877-85.

50. Okuma T, Kishimoto A. A history of investigation on the mood stabilizing effect of carbamazepine in Japan. Psychiatry & Clinical Neurosciences. 1998;52:3-12.

51. Walden J, Grunze H, Bungmann D, Liu Z, Dusing R. Calcium antagonist effects of carbamazeine as a mechanism of action in neuropsychiatric disorders. Studies in calcium dependent model epilepsies. European Neuopsychopharmacol. 1992;2:455-62.

52. Walden J, Grunze H, Mayer A, Dusing R, Schirmacher K, Liu Z, et al. Calcium antagonistic effects of carbamazepine in epilepsies and affective psychoses. Neuropsychobiology. 1993;27:171-5.

53. Bowden CL, Brugger AM, Swann AC. Efficacy of divalproex vs lithium in the treatment of mania. JAMA. 1994;271:918-24.

54. Kazuno A, Munakata K, Kato N, Kato T. Mitochondrial DNA-dependent effects of valproate on mitochondrial calcium levels in transmitochondrial cybrids. International Journal of Neuropsychopharmacology. 2008;11:71-8.

55. Kurita M, Nishino S, Ohtomo K, Rai M, Shirakawa H, Mashiko H, et al. Sodium valproate at therapeutic concentrations changes Ca2+ response accompanied with its weak inhibition of protein kinase C in human astocytoma cells. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2007;31(600-604).

56. Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur Neuropsychopharmacol. 2012;22:339-46.

57. von Wegerer J, Hesslinger B, Berger M, Walden J. A calcium antagonistic effect of the new antiepileptic drug lamotrigine.

European Neuropsychopharmacology. 1997;7(2):77-81.

58. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disorders. 2013;15:1-44.

59. Putney JW. Pharmacology of capacitative calcium entry. Molecular Interventions. 2001;1(2):84-94.

60. Sica D. Calcium channel blocker class heterogeneity: select aspects of pharmacokinetics and pharmacodynamics. J Clin Hypertension. 2005;7, Suppl 1(4):21-6.

61. Doran AR, Narang PK, Meigs CY. Verapamil concentrations in cerebrospinal fluid after oral administration. N Engl J Med. 1985;312:1261-2.

62. Yamashita A, Ozaki A, Ikegami A, Hayashi A, Hara H, Sukamoto T, et al. Effects of a new diphenylpiperazine calcium antagonis, KB-2796, on cerebral ischemic neuronal damage in rats. General Pharmacology. 1993;25:1473-80.

63. Maniskas ME, Roberts JM, Aron I, Fraser JF, Bix GJ. Stroke neuroprotection revisited: Intra-arterial verapamil is profoundly neuroprotective in experimental acute ischemic stroke. Journal of Cerebral Bood Flow & Metabolism. 2016;36:721-30.

64. Dubovsky SL, Franks RD, Lifschitz M. Effectiveness of verapamil in the treatment of a manic patient. AmJPsychiatry. 1982;139:502-4.

65. Dubovsky SL, Franks RD, Schrier D. Phenelzine-induced hypomania: Effect of verapamil. BiolPsychiatry. 1985;20:1009-14.

66. Barton BM, Gitlin MJ. Verapamil in treatment-resistant mania: An open trial. JClinPsychopharmacol. 1987;7:101-3.

67. Gitlin MJ, Weiss JC. Verapamil as maintenance treatment in bipolar illness: A case report. J Clin Psychopharmacol. 1984;4:341-3.

68. Mathis P, Schmitt L, Moron P. Efficacy of verapamil in mania crisis. Encephale. 1988;14(3):127-32.

69. Wisner KL, Peindl KS, Perel JM, Hanusa BH, Piontek CM, Baab S. Verapamil treatment for women with bipolar disorder. Biol Psychiatry. 2002;51:745-52.

70. Dubovsky SL, Franks RD, Allen S, Murphy J. Calcium antagonists in mania: A double-blind study of verapamil. Psychiatry Res. 1986;18:309-20.

71. Dose M, Emrich HM, Cording-Tommel C. Use of calcium antagonists in mania. Psychoneuroendocrinology. 1986;11:241-3.

72. Giannini AJ, Houser WL, Loiselle RH. Antimanic effects of verapamil. AmJPsychiatry. 1984;141:1602-3.

73. Garza-Trevino ES, Overall JE, Hollister LE. Verapamil versus lithium in acute mania. AmJPsychiatry. 1992;149:121-2.

74. Giannini AJ, Taraszewski R, Loiselle RH. Verapamil and lithium as maintenance therapy of manic patients. JClinPharmacol. 1987;27:980-2.

75. Hoschl C, Kozeny J. Verapamil in affective disorders: a controlled, doubleblind study. Biol Psychiatry. 1989;25(2):128-40.

76. Giannini AJ, Loiselle RH, Price WA. comparison of antimanic efficacy of clonidine and verapamil. JClinPharmacol. 1985;25:307-8.

77. Mallinger AG, Thase ME, Haskett R, Buttenfield J, Luckenbaugh DA, Frank E, et al. Verapamil augmentation of lithium treatment improves outcome in mania unresponsive to lithium alone: prelminary findings and a discussion of therapeutic mechanisms. Bipolar Disorders. 2008;10:856-66. 78. Kastner T, Friedman DL. Verapamil and valproic acid treatment of prolonged mania. JAmAcadChild AdolPsychiatry. 1992;31:271-5.

79. Silverstone PH, Birkett L. Diltiazem as augmentation therapy in patients with treatment-resistant bipolar disorder: a retrospective study. Journal of Psychiatry & Neuroscience. 2000;25:276-80.

80. Caillard V. Treatment of mania using a calcium antagonist- preliminary trial. Neuropsychobiology. 1985;14:23-6.

81. de Leon OA. Response to nimodipine in ultradian bipolar cycling after amygdalohippocampectomy. J Clin Psychopharmacology. 2012;32:146-8.

82. Davanzo PA, Krah N, Kleiner J, McCracken J. Nimodipine treatment of an adolescent with ultradian cycling bipolar affective illness. JChild AdolPsychopharmacol. 1999;9:51-61.

83. Pazzaglia PJ, Post RM, Ketter TA, Callahan AM, Marangell LB, Frye MA, et al. Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. JClinPsychopharmacol. 1998;18:404-13.

84. Hesslinger B, Riedel H, Hellwig B, Walden J, Berger M. Phase prevention in bipolar affective disorder with nimodipine. A case report. Nervenartz. 1996;67(5):394-6.

85. Post RM, Frye MA, Denicoff KD, Leverich GS, Dunn RT, Osuch EA, et al. Emerging trends in the treatment of rapid cycling bipolar disorder: a selected review. Bipolar Disorders. 2000;2:305-15.

86. Goodnick PJ. The use of nimodipine in the treatment of mood disorders. Bipolar Disorders. 2000;2 (3 Pt 1):165-73.

87. Manna V. Disturbi affectivi bipolari e ruolo del calcio intraneuronale. Effetti terapeutici del trattamento con cali di litio e/o calcio antagonista in pazienti con rapida inversione di polarita. Minerva Medicaa. 1991;82:757-63.

88. Walton SA, Berk M, Brook S. Superiority of lithium over verapamil in mania: a randomized, controlled, singleblind trial. JClinPsychiatry. 1996;57(11):543-6.

89. Janicak PG, Sharma RP, Pandey G, Davis JM. Verapamil for the treatment of acute mania: a double-blind, placebocontrolled trial. Am J Psychiatry. 1998;155:972-3.

90. Dubovsky SL, Lee C, Christiano J, Murphy J. Elevated platelet intracellular calcium concentration in bipolar depression. Biol Psychiatry. 1991;29(5):441-50. 91. Dubovsky SL. Beyond the serotonin reuptake inhibitors: rationales for the development of new serotonergic agents. JClinPsychiatry. 1994;55[2.suppl]:34-44.

92. Kulkarni J, Garland KA, Scaffidi A, Headey B, Anderson R, de Castella A, et al. A pilot study of hormone modulation as a new treatment for mania in women with bipolar affective disorder.
Psychoneuroendocrinology. 2006;31:543-7.
93. Elliott ML, Romer A, Knodt AR, Hariri AR. A connectome-wide functional signature of transdiagnostic risk for mental illness. Biol Psychiatry. 2018;84:452-9.