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Role of Protein Kinase C in Bipolar Disorder: A Review of the Current Literature

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Abstract
Bipolar disorder (BD) is a major health problem. It causes significant morbidity and imposes a burden on the society. Available treatments help a substantial proportion of patients but are not beneficial for an estimated 40–50%. Thus, there is a great need to further our understanding the pathophysiology of BD to identify new therapeutic avenues. The preponderance of evidence pointed towards a role of protein kinase C (PKC) in BD. We reviewed the literature pertinent to the role of PKC in BD. We present recent advances from preclinical and clinical studies that further support the role of PKC. Moreover, we discuss the role of PKC on synaptogenesis and neuroplasticity in the context of BD. The recent development of animal models of BD, such as stimulant-treated and paradoxical sleep deprivation, and the ability to intervene pharmacologically provide further insights into the involvement of PKC in BD. In addition, the effect of PKC inhibitors, such as tamoxifen, in the resolution of manic symptoms in patients with BD further points in that direction. Furthermore, a wide variety of growth factors influence neurotransmission through several molecular pathways that involve downstream effects of PKC. Our current understanding identifies the PKC pathway as a potential therapeutic avenue for BD.

Introduction

Bipolar disorder (BD) is a chronic and life-threatening disorder, and has been identified as one of the leading causes of disability worldwide [1]. BD is classically characterized by recurrent fluctuation between distinct periods of both positive (mania) and negative (depression) extremes of mood state. Additional features frequently associated with BD are impairment in emotion perception, affect regulation, attention, and executive function-

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ing [2]. These impairments also correlate with structural and functional abnormalities in frontolimbic brain regions, such as prefrontal cortex (PFC), hippocampus, and amygdala, that regulate emotion, memory, and motivated behavior [3]. Despite its heavy toll on human lives, the molecular mechanisms underlying the pathogenesis of BD remain elusive.

Initial insights into the pathophysiology BD were gained in 1980s after the serendipitous discovery of lithium [4] and valproic acid [5] as effective mood stabilizers. In the past 10 years, several animal models of mania have been developed to mimic human BD [6]. The manic phenotype is usually induced in animal models by pharmacological (amphetamine [AMPH] and ouabain), environmental (paradoxical sleep deprivation [PSD]), and genetic (black Swiss mice) interventions [6]. These interventions induce behavioral changes that are analogous to manic symptoms, such as hyperlocomotion [7], insomnia, risk-taking behavior [8], and increased appetitive 50-kHz ultrasonic vocalizations (USV; a marker for euphoric mood and pressured speech) [9]. These models are tested for their face (animals mimicking manic symptoms), construct (correlation of similar pathophysiological alteration at molecular level), and predictive (amelioration of symptoms by currently accepted treatments of mania) validity to enhance our understanding of BD [10]. Our advances in neuroimaging techniques, such as in vivo magnetic resonance imaging, and novel genetic approach, such as convergent functional genomics, are providing us endophenotypic characteristics of BD [11]. After 3 decades of intensive preclinical and translational research, protein kinase C (PKC) has come to be recognized to play a central role in the pathophysiology of BD [12–14].

The protein kinase family of proteins is one of the largest superfamily of nearly 500 proteins that are evolutionarily conserved across 11 eukaryotic species and regulate various cellular events [15, 16]. The PKC family includes 10 serine/threonine protein kinases that are encoded by 9 mammalian genes and reversibly phosphorylate serine, threonine, and tyrosine residues in their target proteins [15]. These 10 kinases are subdivided into 3 subfamilies based on their structure and their regulatory cofactors, namely classical or conventional PKC [cPKC: α, β_I, β_{II}, and γ; regulated by phospholipids, Ca^{2+} ions, and diacylglycerol (DAG)], novel PKC (nPKC: ε, δ, η, θ, and μ; regulated by phospholipid and DAG), and atypical PKC (aPKC: ξ, Mξ, ι, and λ; regulated by phospholipids but are independent of DAG and Ca^{2+} ions) [17]. All PKCs consist of a highly conserved C-terminal catalytic domain and a nonconserved N-terminal regulatory domain [18].

In the CNS, cPKC subfamily enzymes, PKCα, -β, and -γ, are most abundantly expressed [19] and influence neuronal signaling by short-term (neurotransmitter release and ion fluxes), medium-term (receptor regulation), and long-term (cell proliferation, synaptic remodeling, and gene expression) mechanisms [20]. PKC isozymes are highly expressed in the frontolimbic structures, such as PFC, hippocampus, and amygdala, which are involved in mood regulation [21, 22]. PKC is inhibited by mood stabilizers such as lithium and valproic acid [14]. Additionally, PKC signaling is involved in the regulation of processes that are affected in BD, such as neuronal excitability [23], neurotransmitter release [24, 25], glutamatergic neurotransmission [26], neuroplasticity [27], apoptotic pathway activation [28], mitochondrial dysfunction, and oxidative stress [29], and neuroinflammation [30–32].

We searched PubMed database with key words "protein kinase C bipolar disorder" and "PKC bipolar disorder" and selected articles since 2008. Few earlier manuscripts are tabulated in the article to provide a historical context of recent observations. We reviewed a total of 26 studies (9 in vitro, 11 in vivo, and 6 clinical studies). We organized our narrative to address proposed pathophysiological mechanisms underlying BD, including: (1) PKC translocation and activity; (2) putative downstream molecular effects, and (3) gene candidates. The studies are indexed in Tables 1–4.

PKC Translocation and Activity

Preclinical Studies

The importance of hyperactive PKC signaling in BD was first appreciated when commonly used mood stabilizers, both lithium and valproic acid, were observed to inhibit PKC activity in vitro [33, 34] and in vivo [35–37]. Later, the levels of membrane-associated PKC were shown to decrease after exposure to lithium and valproic acid, in vitro [38] and in vivo [39, 40]. These observations were corroborated in humans when chronic treatment with lithium decreased PKC signaling in euthymic patients with BD [41]. One of the mechanisms underlying this mitigation of PKC hyperactivity by lithium and valproic acid is the inhibition of its translocation from cytosol to cell membrane. PKC is known to translocate to cell membrane when stimulated by phorbol esters (phorbol 12-myristate 13-acetate [PMA]), serotonin (5HT), K^+ ions [42], and DAG analogs in vitro [43] and ex vivo [34]. It has been shown that platelets from patients in acute

Table 1. Summary of the in vitro studies

First author [Ref.], year	Model	Design	Duration	Main findings
Chen [38], 1994	C6 glioma cell line	Valproic acid exposure 0.6 nM	6–7 days	Decreased PKC alpha and epsilon (not delta or zeta) in both membrane and cytosolic compartment; increased cytosolic/membrane ratio of PKC activity
Kirshenboim [132], 2004	HEK 293 and PC12 cell line	Lithium treatment 0–20 mM	0–6 h	Lithium increased inhibition of GSK-3beta by increasing phosphorylation of inhibitory site of GSK-3beta (Ser 9) in HEK 293 and PC12 cells via PI3-PKC signaling; lithium increased PKC alpha activity twofold in both cell lines
Kim [102], 2009	Cultured hippocampal neurons	Lithium treatment 5.0 mM	4 h	Lithium increased number of functional synapses in cultured hippocampal neurons via action of glutamate on postsynaptic receptors; no change in PKC activity reported
Ou [101], 2009	PC12 cell line and human astrocytes	Lithium treatment 100 mM	12 h	Lithium elongates cilia in PC12 and human astrocytes via cAMP signaling pathway
Rittiner [158], 2014	HEK 293 cell line	Overexpressed mouse DGKη in human embryonic kidney 293 cells	–	DGKeta reduces PKC activation and enhances GPCR signaling

mania show enhanced 5HT-induced PKC translocation and membrane-bound PKC activity than controls, which is reversed after lithium treatment [44]. Brain slices from lithium-fed rats displayed inhibited stimulus-induced membrane translocation of PKC without affecting its baseline activity [42]. Moreover, PKC is pharmacologically activated by PMA, which provides DAG substitute [45]. PKC activation by direct infusion of PMA in the PFC of rodents and monkeys was shown to induce distractibility, impaired judgment, impulsivity, and thought disorder, which are characteristic symptoms of BD [46]. Furthermore, in rodents, infusion of PMA in the hippocampus, but not in lateral ventricle, was also found to have antidepressant-like effects, and induce enhanced risk-taking behavior [8].

With the development of animal models of mania in the past 2 decades, the involvement of PKC in manic phenotype has become more apparent. Increased PKC activity is observed in the PFC of rats submitted to AMPH administration [47, 48]. AMPH-induced hyperlocomotion has been shown to be reversed [7] and prevented [49] by intraperitoneal administration of lithium or tamoxifen (TMX), a selective estrogen receptor modulator with PKC inhibitory activity [8, 50]. Similarly, intraperitoneal administration of quercetin, a nonspecific PKC inhibitor, also prevented methylphenidate-induced hyperlocomotion [51]. Not only in the presence of pharmacological intervention, daily intraperitoneal administration of lithium or TMX alone for 7 days significantly decreases phosphorylated PKC (pPKC) in the hippocampus, PFC, amygdala, and striatum [7]. Furthermore, chronic administration (14 days) of TMX caused depressive-like behavior in the forced swim test, and resulted in a reduction of cell proliferation in the dentate gyrus of the hippocampus [8].

Sleep-deprived rats display paradoxical hyperlocomotion, increased penile erection, and insomnia [48]. Sleep-deprived animals did not display manic phenotype when they were pretreated with lithium or TMX or their combination [52]. Intraperitoneal administration of quercetin also prevented PSD-induced hyperlocomotion [53]. Interestingly, PSD-induced behavioral changes were reversed by a one-time administration of lithium about 1 h prior to behavioral testing without affecting baseline activity [48]. At cellular level, PSD decreased hippocampal cell proliferation as indicated by decreased bromodeoxyuridine labeling [48]. Again, single administration of lithium increased BrdU-labeled hippocampal neurons in sleep-deprived rats highlighting potent neuroprotective actions of lithium [48].

Table 2. Summary of the in vivo studies

First author [Ref.], year	Model	Design	Duration	Main findings
Wang [34], 1989	Rat brain parietal cortical slices	Phorbol ester (PKC activator)	20-min incubation	Induced dose-dependent increase in K^+ induced 5HT release from cortical slices; this phorbol ester facilitation was prevented by PKC inhibitor
Chen [39], 2000	Male Sprague-Dawley rats and Male C57 BL/6 mice	Lithium and VPA treatment	3–4 weeks	Lithium and VPA decreased plasma membrane-associated PKC alpha and PKC epsilon, increased DNA binding of AP-1 and expression of AP-1-regulated genes
Wang [42], 2001	Male Sprague-Dawley rats	Food pellets containing 0.212% (w/w) lithium chloride	3 or 6 weeks	In brain slices, lithium treatment inhibited PMA-, 5HT-, or potassium-induced PKC translocation from cytosol to membrane without affecting basal membrane or cytosolic PKC activity
Kirshenboim [132], 2004	C57Bl/6J mice	ICV injection of lithium	3 h	ICV injection of lithium increased GSK-3beta Ser-9 phosphorylation and enhanced PKC alpha activity by 1.8-fold in mouse hippocampus
Szabo [47], 2009	Amphetamine-induced mania; imipramine-induced mania; paradoxical sleep deprivation	Lithium treatment 1.2 and 2.4 g/kg	4 weeks	PKC activity was increased in sleep-deprived and amphetamine-treated rats; increased PKC mediated phosphorylation of neurogranin, NMDA receptor site GluN1S896, and AMPA receptor site GluA1T840 in PFC of sleep-deprived and imipramine-treated rats; effects were reversed in lithium-treated animals; imipramine treatment enhanced phospho-MARCKS in PFC
Barbier [167], 2009	PKCI/HINT1 knockout mice	–	–	PKCI/HINT1 knockout mice display anxiolytic-like and anti-depressant like behavior and elevated corticosterone in plasma
Hains [174], 2009	Chronic stress model; male Sprague–Dawley rats	Chelerythrine 1.0 mg/kg s.c.	21 days	PKC inhibition prior to daily stress, protected working memory and distal apical dendritic spine loss in lay II/III pyramidal neurons (greater spine density) of rat prelimbic cortex induced by daily stress
Cechinel-Recco [7], 2012	Amphetamine-induced mania	Lithium (47.5 mg/kg) and TMX (1 mg/kg), i.p.	Reversal model (7 days); prevention model (14 days)	Lithium and TMX reversed and prevented d-AMPH-induced hyperactivity; lithium and TMX treatment reversed and prevented the increase in PKC alpha phosphorylation induced by d-AMPH
Armani [52], 2012	Paradoxical sleep deprivation	Lithium (50–150 mg/kg) and TMX (0.5–2.0 mg/kg)	9 days	Sleep deprivation induced hyperactivity in mice that was prevented by lithium, TMX and combination treatment
Steckert [50], 2012	Amphetamine-induced mania	TMX (1 mg/kg), i.p.	Reversal model (7 days); prevention model (14 days)	TMX reversed and prevented d-AMPH induced behavioral effects via inhibition of PKC and prevention of oxidative stress

Table 2 (continued)

First author [Ref.], year	Model	Design	Duration	Main findings
Abrial [8], 2013	Amphetamine-induced mania	TMX (10 or 80 mg/kg, i.p.) and chelerythrine (3 mg/kg s.c.); PMA (intracerebrally administered acutely)	TMX and chelerythrine (60 min before the AMPH) PMA (40 or 10 min before the test)	TMX and chelerythrine prevented AMPH-induced hyperactivity and risk taking behavior, and caused depressive-like behavior; PMA (PKC activator) had antidepressant-like effects
Pereira [9], 2014	Amphetamine-induced mania	TMX (1 mg/kg), lithium (100 mg/kg), and myricitrin (10 and 30 mg/kg)	–	TMX, lithium, and myricitrin (PKC inhibitor) reduced appetitive 50-kHz calls (proposed to be model euphoric mood and pressured speech of human mania)
Abrial [48], 2014	Paradoxical sleep deprivation in rats	PKC inhibitors	Acute injection	PSD induced mania, increased SNAP 25 in hippocampus and PFC suggesting PKC hyperactivity; PKC inhibitors attenuated manic behavior and rescued hippocampal cell proliferation deficits induced by PSD
Kanazawa [53], 2016	Paradoxical sleep deprivation; male Swiss mice	Quercetin (10 or 40 mg/kg, i.p.)	Acute injection	PSD-induced hyperactivity and lipid peroxidation in PFC, hippocampus, and striatum were prevented by quercetin
Kanazawa [51], 2017	Methylphenidate-induced mania	Lithium (100 mg/kg) and diazepam (5 mg/kg)	Acute and chronic (21 days) protocol	Acute and 21 days of treatment with lithium and diazepam reversed methylphenidate-induced hyperlocomotion and oxidative stress in PFC, hippocampus, and striatum; quercetin blocked methylphenidate-induced hyperactivity without affecting spontaneous locomotor activity

5HT, serotonin; VPA, valproic acid; AP-1, activator protein 1; PMA, phorbol 12-myristate, 13-acetate; GSK, glycogen synthase kinase; PSD, paradoxical sleep deprivation; PKCI/HINT1, PKC interacting protein/histidine triad nucleotide binding protein 1; AMPH, amphetamine; d-Amph, dextro-amphetamine; TMX, tamoxifen; PFC, prefrontal cortex; SNAP, synaptosomal-associated protein 25.

Pereira et al. [9] observed that AMPH increases appetitive 50-kHz USV. The USV are emitted by rodents in association with social communication and reward behavior such as mating [54]. The authors, hence, reasonably propose that AMPH-induced increase in USV simulates euphoric affect and pressured speech that is observed in patients with BD during acute mania [9]. In support of its predictive validity, pretreatment of rats with Li or TMX blocked the increase in USV calls induced by AMPH without affecting spontaneous call rates or locomotor activity [9]. Myricitrin, another PKC inhibitor, also prevented the increased USV induced by AMPH in a dose-dependent manner without affecting baseline call rate at any of the doses used [9].

PKC is also commonly inhibited by chelerythrine, a benzophenanthridine alkaloid that was identified as a selective PKC inhibitor in 1990 [55]. Since then, it is widely used to investigate the role of PKC in several biological systems such as neuro- and cancer biology [56]. After several years of controversy regarding its selectivity [57–59], it has recently been shown that chelerythrine influences intracellular calcium homeostasis independent of PKC [60]. In animal models of mania, administration of chelerythrine prevented manic phenotype induced by AMPH [8]. While inhibition of PKC was concluded as the underlying mechanism by the authors, it is plausible that its effect on calcium homeostasis may have been involved in this observation [61]. In support of this alternative expla-

Table 3. Summary of the human studies

First author [Ref.], year	Sample	Main findings
Friedman [44], 1993	Platelets from patients with BD	Increased PKC activity in manic patients; lithium treatment decreased PKC activity in plasma membrane and cytosolic fractions
Wang [65], 1996	Postmortem cortical homogenate	Increased PKC level and membrane-bound PKC activity in samples from patients with BD in comparison with healthy controls
Wang [68], 1999	Platelets from patients with BD	Basal PKC activity in platelets BD patients during acute manic episode was higher in membrane fraction than control, depressed, or schizophrenic subjects
Soares [69], 2000	Platelets from patients with BD	Platelets from lithium-treated euthymic BD patients had lower cytosolic PKC alpha isozyme and PIP2 membrane levels
Wang [67], 2001	Postmortem cortical homogenate	Increased RACK-1 association (membrane anchor) of PKC in samples from patients with BD in comparison with healthy controls
Pandey [171], 2002	Platelets from patients with BD	Platelets had decreased expression of PKC alpha, beta-I, beta-II, and PLC delta isozyme in membrane and cytosol fractions but not of unipolar depression; however, MARCKS was significantly elevated in membrane and cytosol fraction in patients with BD
Hahn [175], 2005	Platelets from patients with BD	Platelets from BD patients have increased basal membrane to cytosol PKC ratio in comparison to control; BD subjects had higher translocation of PKC with serotonin, thrombin, and PMA in comparison with control; lithium and VPA attenuated stimulus induced translocation of PKC
Akimoto [176], 2007	Platelets from patients with BD	Exaggerated PKC stimulation induced calcium influx; in controls PKC had inhibitory effect on calmodulin system regulated capacitive calcium entry; in BD subjects, this inhibitory effect of PKC was enhanced
Pandey [177], 2008	Platelets from pediatric patients with BD	Platelets had decreased expression and activity of PKC beta-I, beta-II, but not PKC alpha or PKC delta; 8 weeks of treatment with mood stabilizers normalized or increased these observations
Perlis [170], 2010	Genome-wide association study	Suicide attempt in BD patients: GWAS meta-analysis of 8,700 mood disorder subjects identified association with multiple loci including PKC epsilon
Carroll [141], 2010	Genetic linkage study	SNP in PKC alpha may play a role in pedigree analysis of psychotic and mood disorder
Kandaswamy [142], 2012	Genetic linkage study	Genotyped 4 microsatellite markers and 9 SNPs; PKC zeta may play a role in susceptibility to BD
Le-Niculescu [172], 2013	Convergent functional genomics	(1) No SI to high SI – differentially expressed genes are identified; (2) CFG – prioritize genes to relevance to suicidality; (3) expression of these genes in blood of live BD vs. suicide completers; found 13/41 show relevance from no SI to high SI to completers, 6/13 significant; (4) SAT1, PTEN, MARCKS, MAP3K3 differentiated past and future hospitalization in patients with BD
Kittel-Schneider [163], 2016	Proof of concept study: mRNA from peripheral blood and fibroblasts of heterozygote DGKH risk variants carrier with BD and non-risk variant carriers with and without BD	DGKH1 expression was increased in peripheral blood of risk variant carriers; PKCD expression was significantly elevated in fibroblasts from DGKH risk variant carriers; current depressive episode had lower PKC delta levels, and lithium treatment was found to be associated with elevated PKC alpha levels

BD, bipolar disorder; PIP2, phosphatidylinositol-4,5-bisphosphate; RACK-1, receptor for activated C kinase-1; PLC, phospholipase C; MARCKS, myristoylated alanine-rich C-kinase substrate; PMA, phorbol esters (phorbol 12-myristate 13-acetate); GWAS, genome-wide association study; SNP, single nucleotide polymorphism; SI, suicidal ideations; SAT1, spermidine/spermine N1-acetyltransferase; PTEN, phosphatase and tensin homolog (PTEN); MAP3K3, mitogen-activated protein kinase kinase kinase 3; DGKH, gene coding for diacylglycerol kinase; PKCD, gene coding for PKC delta; CFG, convergent functional genomics; VPA, valproic acid.

Table 4. Summary of the clinical studies

First author [Ref.], year	Study	Mood state	Treatment	Duration	Observation
Bebchuk [73], 2000	Proof of concept study	Mania	Single-blind, open-label, add-on (some patients were on no other medications)		Rapid resolution of manic symptoms
Kulkarni [78], 2006	Pilot study: double-blind, placebo controlled (n = 13)	Mania or hypomania	Group 1: TMX 40 mg/day; group 2 MPA 20 mg/day; and group 3 placebo; adjunct to lithium or VPA	28 days	Mean CARS-M score change at the end of trial: group 1 = –22.2± 12.49, group 2 = –13.0±10.76, group 3 = –8.50±7.3; 1 vs. 3 p < 0.05, 2 vs. 3 p < 0.01, 1 vs. 2 p > 0.05
Zarate [76], 2007	Double-blind, placebo controlled (n = 16)	Mania or mixed state	TMX monotherapy (20–140 mg/day)	21 days	63% response in TMX vs. 13% in placebo group
Yildiz [75], 2008	Double-blind, placebo controlled (n = 50)	Mania or mixed state	TMX 80 mg/day vs. placebo; lorazepam: pro re nata use of lorazepam up to 5 mg/day allowed, avoided after 12 days, and not administered 12 h prior to YMRS	21 days	Mean decrease in YMRS: TMX = 5.84±0.64/week vs. placebo = 1.5± 0.73/week, p < 0.001
Amrollahi [79], 2011	Double-blind, placebo controlled (n = 40)	Mania	Group A: lithium (1–1.2 mEq/L) + TMX (80 mg/day); group B: lithium (1–1.2 mEq/L) + placebo	42 days	YMRS score – group A = 3.15± 1.78, group B = 9.45±8.50; p < 0.01
Kulkarni [77], 2014	Double-blind, placebo controlled (n = 51)	Mania	Group 1: TMX 40 mg/day; group 2 MPA 20 mg/day; and group 3 placebo; adjunct to lithium, VPA, or carbamazepine, and/or mood-stabilizing antipsychotic	28 days	CARS-M scores decreased more quickly in group 2 (MPA); no significant difference in mean CARS-M score change across groups at the end of trial; MPA but not TMX was beneficial in treating acute mania in women
Yildiz [87], 2016	Double blind, placebo controlled (n = 48)	Mania	MRS scan at baseline and after 3 weeks of treatment	21 days	TMX increased marker of brain energy metabolism (total creatinine) and neuronal viability (NAA) in the dorsomedial PFC
Ahmad [82], 2016	Double blind, active-controlled trial (n = 84)	Mania or mixed state	Endoxifen (4 mg/day or 8 mg/day) or divalproex (1,000 mg/day) in a 2:1 ratio	21 days	Significant decrease in YMRS score in as early as 4 days in endoxifen group; the effect remained significant throughout 21 days. Response rate 45 and 65% at 4 and 8 mg/day of endoxifen treatment, respectively.
Talaei [13], 2016	Meta-analysis of 5 randomized controlled trials	n.a.	n.a.	n.a.	TMX monotherapy-associated difference in mean mania score change was 22.09 (p < 0.01); pooled odds ratio of response to TMX was 15.36 (95% CI, 2.99–78.73; p = 0.001)

CARS-M, Clinician administered rating scale – Mania; MPA, medroxyprogesterone; TMX, tamoxifen; YMRS, Young Mania Rating Scale; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; VPA, valproic acid; PFC, prefrontal cortex.

nation, increased intracellular Ca^{2+} ions have been observed in BD [40, 62, 63]. Verapamil, a calcium channel blocker with PKC inhibitory activity, is reported to significantly improve manic symptoms when combined with lithium [64].

Clinical Studies

In patients with BD, PKC activity is studied mostly in the postmortem brain sample and platelets (usually during acute manic episode). A study in cortical homogenates of patients with BD showed that PKC levels and membrane-bound PKC activity were found to be increased in comparison with healthy controls [65]. PKC is anchored in the membrane by receptor for activated C kinase-1 (RACK-1) [66]. In frontal cortical homogenate, membrane PKC was found to be associated more with RACK-1 in BD samples [67]. Furthermore, in vitro stimulation of PKC by PMA produced enhanced stimulus-induced association between PKC and RACK-1 in samples from BD subjects in comparison to matched controls [67]. Platelets from manic patients also show higher membrane-bound PKC activity in comparison with healthy controls and patients with depression and schizophrenia [40, 68]. Moreover, chronic treatment with lithium has been observed to decrease both cytosolic and membrane-bound PKC levels in platelets from patients with BD [69].

Further support to PKC hyperactivity in BD is drawn from the use of TMX in human BD patients. TMX is a prodrug with little affinity towards estrogen receptor, but its metabolites have high affinity and compete with estrogen for binding [70]. TMX also displays PKC inhibitory activity [71] and is the only PKC inhibitor that crosses the blood brain barrier [72]. In 2000, Bebchuk et al. [73] reported a proof-of-concept study in which TMX resolved acute manic symptoms in humans for the first time. Since then, several small-scale clinical trials have been conducted to test the utility of TMX in BD management [74–77]. Patients with BD managed with TMX for 3 weeks showed a marked improvement in their manic presentation in as early as 5 days, an effect that remained significantly different throughout the 3-week trial [76]. TMX is also effective as an adjunct to lithium or valproic acid [78]. In a longer double-blind, randomized, placebo-controlled 6-week study, it was demonstrated that the combination of TMX with Li was superior to Li alone for the rapid reduction of manic symptoms [79]. Furthermore, TMX has also been reported to be an effective antimanic treatment in pediatric population [80]. In a recent meta-analysis, TMX was found to be effective as monotherapy and as an adjunctive treatment for manic symptoms [13]. Recently, monotherapy with endoxifen, a metabolite of TMX and a potent PKC inhibitor [81], was found to be as effective as with valproic acid (extended release 1,000 mg/day) in mitigation of manic symptoms [82]. Interestingly, medroxyprogesterone acetate, a progestin, also shows significant improvement in mania symptoms and may have a therapeutic utility in the future [77, 78].

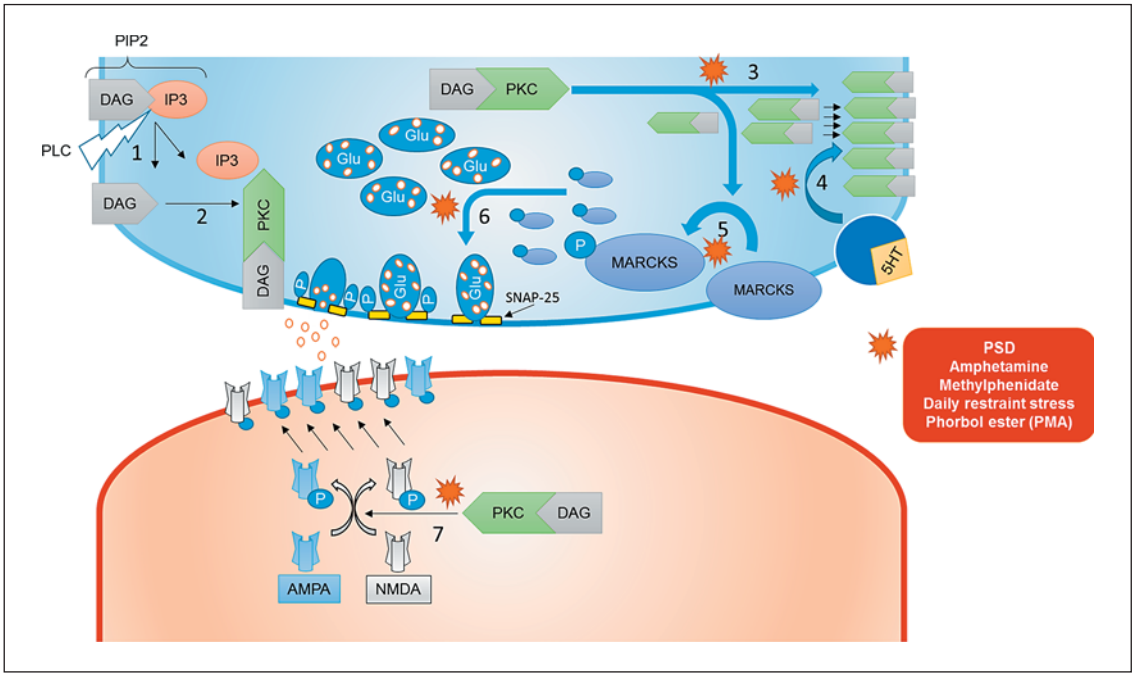
BD is also associated with inefficient energy homeostasis in the brain, including decreases in mitochondrial respiration, high-energy phosphates, pH, along with changes in mitochondrial morphology, increases in mitochondrial DNA polymorphisms, downregulation of nuclear mRNA molecules and proteins involved in mitochondrial respiration [83–85], and decreased neuronal viability marker, N-acetylaspartate (NAA) [86]. Recently, in a double-blind placebo-controlled magnetic resonance spectroscopy study, TMX was shown to increase total creatinine and NAA in dorsomedial PFC in patients with BD, suggesting enhanced neuronal viability [87].

In contrast to putative hyperactive PKC signaling in BD, Young et al. [88] did not observe any significant difference in PKCα levels and activity between platelets from control, drug-free BD patients, and lithium-treated BD patients. In another contradictory finding in a recent report, Hayashi et al. [61] reported increased PKC activity in response to lithium in cultured adipocytes from patients with BD. These conflicting observations could be due to differences in patient characteristics and differences in tissues studied, respectively. In addition, the latter observation also implies that lithium may have tissue-specific actions on PKC signaling.

Downstream Targets of PKC

In addition to corroborating hyperactive PKC signaling in BD, studying downstream targets of PKC in BD may yield additional therapeutic targets. We will discuss recent work that has identified key downstream substrates of PKC such as neurogranin, neurotrophic factors (NTFs), growth-associated protein 43 (GAP-43; and several aliases such as B-50, F1, and neuromodulin), myristoylated alanine-rich C-kinase substrate (MARCKS), synaptosomal-associated protein 25 (SNAP-25), along with effect of PKC on glutamatergic neurotransmission, oxidative stress, apoptotic, and cyclic AMP signaling (Fig. 1).

Neurogranin is a brain-specific calmodulin-binding protein that is expressed in the dendritic spines [47]. Neu-



Color version available online

Fig. 1. Hypothetical schema of the effects of hyperactive protein kinase C (PKC) signaling in an animal model of bipolar disorder. 1, activated phospholipase C dissociates phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol triphosphate (IP3); 2, DAG as a cofactor activates PKC; 3, increased insertion of PKC in the membrane; 4, increased stimulus-induced membrane translocation of PKC; 5, increased myristoylated alanine-rich C-kinase substrate (MARCKS) phosphorylation; 6, increased membrane alignment of neurotransmitter-containing vesicles; 6, increased phosphorylation of synaptosomal-associated protein 25 (SNAP-25) and increased neurotransmitter release; 7, increased alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor phosphorylation and membrane insertion; P, monophosphate/phosphorylation; 5HT, serotonin; Glu, glutamate; PSD, paradoxical sleep deprivation; PMA, phorbol esters (phorbol 12-myristate 13-acetate); PLC, phospholipase C.

rogranin is also a postsynaptic PKC substrate [89], regulates synaptic plasticity [90], and is implicated in schizophrenia [91, 92]. In both AMPH and PSD models, along with imipramine treated rats, phosphorylation of neurogranin was increased [47]. Interestingly, neurogranin phosphorylation, which is associated with promanic interventions, was reversed by lithium [47]. Moreover, cultured hippocampal neurons have also been observed to lose their dendritic spines in response to sustained activation of PKC [93].

NTFs, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3, are observed to regulate gene expression and regulate synaptic plasticity via PKC signaling [94, 95]. Furthermore, PKC not only acts as a second messenger but BDNF and NGF also modulate the activity of PKC [96, 97]. PKC, in turn, influence the expression of NTFs, such as NGF [98], BDNF [99], and glial cell line-derived neurotrophic factor [100]. These observations underscore the complexity and interdependence of these signaling cascades that fine-tune the synaptic strength. In vivo, AMPH-treated rats show increased PKC but decreased BDNF and NGF expression [7]. This reduction in NTFs was reversed by lithium and TMX [7]. Hence, although lithium may appear to decrease neuroplasticity markers such as MARCKS and GAP-43, it may enhance synaptic strength by increasing NTF expression. In addition, lithium also elongates cilia in PC12 neuronal cells and human astrocytes via cAMP singling pathway [101]. Also, lithium has been observed to promote synapse formation in hippocampus, independent of PKC activity [102]. Hence, lithium may partly influence neuroplasticity through PKC-independent mechanisms.

GAP-43 is also implicated in neurite outgrowth during neuronal differentiation and in synaptic plasticity [103, 104], since loss of function of GAP-43 inhibits neurotransmitter release [105]. GAP-43 is regulated by PKC protein, but it acts as an adaptor that binds to membrane

lipid-rafts [106]. GAP-43 is also expressed in astrocytes and is also regulated by PKC [107]. GAP-43 levels are found to be decreased in postmortem samples of hippocampi from patients with BD in comparison with matched controls indicating impaired neuroplasticity [108]. On the other hand, lithium administration decreases GAP-43 expression in both immortalized hippocampal cell culture and in the frontal cortex and hippocampus through myo-inositol depletion [109]. However, its role in BD pathophysiology remains unknown, since the decrease in GAP-43 could be a treatment effect of lithium or an independent marker of impaired synaptic plasticity in BD. Further research is needed to address these issues.

MARCKS is a membrane-bound actin crosslinking protein that regulates vesicular trafficking and mobility of structural phospholipids such as phosphatidylinositol-4,5-bisphosphate (PIP2) in the membrane plane [110, 111]. MARCKS undergoes dissociation from the membrane and translocates to cytoplasm after phosphorylation by PKC [112]. An increase in PKC-mediated phosphorylation of MARCKS (pMARCKS) in the PFC was observed in AMPH treatment and PSD models of mania [47]. In patients with BD, treatment with tricyclic antidepressants (TCA) can often induce mania [113]. The administration of imipramine, a TCA, in rats increases the pMARCKS in the PFC [47]. Myo-inositol is an important component of PIP2 and provides the building blocks for inositol phosphate-mediated second messenger signaling [114]. Lithium treatment decreases the levels of MARCKS [115] through myo-inositol depletion [109]. Lithium also reversed the increase in pMARCKS in the PFC of AMPH and imipramine-treated and sleep-deprived rodents [47]. Valproic acid actions, on the other hand, are independent of myo-inositol [116] but also decrease MARCKS expression [117]. These observations highlight that although lithium and valproic acid have different mechanisms of actions, they share PKC as a target and affect its downstream signaling.

SNAP-25 is a t-SNARE protein that regulates neurotransmitter release by exocytosis [118] and is a major PKC substrate [119, 120]. PKC activation with PMA has been shown to increase SNAP-25 phosphorylation and redistribute dopamine- and acetylcholine-containing vesicles to plasma membrane, along with increased depolarization-induced dopamine release [121]. Phosphorylation of SNAP-25 was increased in cerebral cortex, hippocampus, and amygdala of mice following cold-water restraint stress [120]. Interestingly, increased phosphorylation of SNAP-25 in both hippocampus and PFC was also seen in a PSD model of mania, suggesting increased neurotransmitter release [48]. In fact, in support of this proposition, euthymic BD patients have been observed to have enhanced dopamine release compared with healthy subjects [122]. The effect of mood stabilizers or TMX on SNAP-25 phosphorylation, however, remains to be studied.

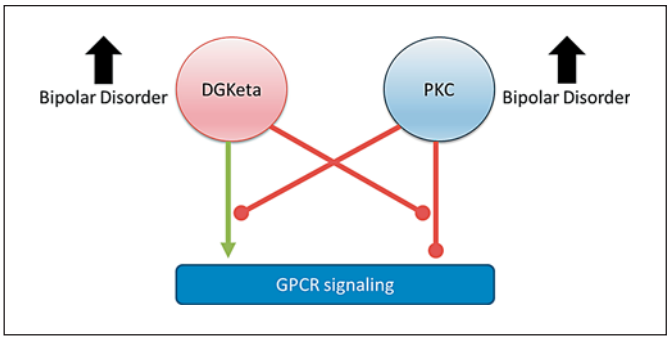
Glutamatergic excitotoxicity is another putative mechanisms proposed in BD pathophysiology [123]. A meta-analysis revealed that glutamate levels were increased in several brain regions of patients with BD [124]. Regarding glutamatergic signaling, AMPH-treated, sleep-deprived, and imipramine-treated rats showed that the increase in the phosphorylation of N-methyl-D-aspartate (GluN1S896) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (GluA1T840) receptor in the PFC was PKC mediated, leading to an increase in trafficking of these receptors to neuronal membranes [47]. Moreover, the same study showed that these events were inhibited by chronic (3-week) lithium treatment, providing another explanation for antimanic properties of lithium [47].

Oxidative stress secondary to mitochondrial dysfunction is also implicated in BD pathophysiology [125]. In a meta-analysis, oxidative stress markers were observed to be increased in BD [126]. Quercetin is a flavanol that contains a polyphenolic structure that scavenges free radicals and hence, acts as an antioxidant, and it also exhibits pleiotropic nonspecific PKC inhibition [127]. Kanazawa et al. [53] showed that the quercetin administration was able to reverse the increase in lipid peroxidation in PFC, hippocampus, and striatum in a mouse model of mania induced by PSD. Quercetin also blocked methylphenidate-induced hyperlocomotion and oxidative stress in PFC, hippocampus, and striatum of mice [51]. It appears that oxidative stress is downstream to PKC signaling as TMX, a selective PKC inhibitor, also prevented and reversed oxidative stress in AMPH-treated rats [50].

GSK-3beta is a constitutively active kinase with high basal activity and inactivated by phosphorylation [128]. GSK was first characterized for its role in glycogen metabolism but later earned its major recognition in developmental and cancer biology [128]. GSK-3beta is inhibited by both lithium [129] and valproic acid [130]. Lithium directly inhibits GSK-3beta at supra-therapeutic levels [131] and indirectly, at therapeutically relevant concentration, through phosphorylation of its key inhibitory site, serine-9 via PI3-PKC pathway [132]. The effect of lithium on GSK-3beta expression, however, may be brain region dependent. For example, in a recent in vivo experiment, we observed that lithium treatment de-

creased total GSK-3beta expression in PFC but increased it in the hippocampus [7]. Nevertheless, AMPH treatment significantly increased GSK-3beta expression and decreased phosphorylated GSK-3beta (pGSD-3beta – inactive form) in all mood-regulating frontolimbic structures [7], suggesting a GSK-3beta hyperactivity. Lithium and TMX administration reversed the AMPH-induced overactivation of GSK-3beta, suggesting that the increase in the GSK-3beta activity may be partly mediated by PKC [7]. Inhibition of GSK has also been shown to be neuroprotective by inhibition of apoptotic signaling and neurodegeneration [133], and is considered as one of the key future therapeutic avenues for BD [134].

The cyclic AMP (c-AMP)/protein kinase A (PKA)/c-AMP response element binding protein (CREB) pathway plays an important role in synaptogenesis and synaptic plasticity [135]. Although the c-AMP /PKA/CREB pathway is not the focus of this review, it is important to note its cross-talk with phospholipase C (PLC)/PKC signaling pathway. The G protein-bound adenylate cyclase catalyzes the conversion of ATP into c-AMP, which activates PKA, which in turn regulates several intracellular processes including phosphorylation of CREB, a transcription factor [136]. Increased c-AMP signaling is also implicated in BD [137–139]. In vivo microdialysis revealed that direct activation of PKC by PMA in the frontal cortex and hippocampus increases c-AMP in the dialysate [39]. Moreover, AMPH-treated rats show a decreased PKA and CREB phosphorylation in the frontolimbic circuit (PFC, hippocampus, amygdala, and striatum), and this decrease was prevented and reversed by lithium and TMX treatment [7].



Color version available online

Fig. 2. Reciprocal regulation of intracellular diacylglycerol kinase eta (DGKeta) and protein kinase C (PKC) activity. DGKeta enhances G-protein coupled receptor (GPCR) signaling, and PKC inhibits GPCR signaling. DGKeta and PKC each reciprocally inhibit this action. Both PKC and DGKeta have been found to be elevated in bipolar disorder.

Genetics

BD has high familial inheritability, and recent advances in genomic studies may provide insights into the genetic basis of BD [140]. Genetic studies have also implicated PKC in BD [141–143]. In the following section, we will briefly discuss putative gene candidates involving activator protein 1 (AP-1), GSK-3beta, DAG kinase eta (DGKeta), and PKC interacting protein/histidine triad nucleotide binding protein 1 (PKCI/HINT1), that highlight putative genetic mechanisms underlying BD.

AP-1 is a transcription factor, comprising Fos and Jun subunits [144], that regulates gene expression and neuroplasticity and is implicated in several chronic cardiovascular [145] and psychiatric illnesses [144]. AP-1 has been shown to increase its DNA binding in response to exposure to lithium and valproic acid [146–148] and increase the translation of AP-1-regulated genes in vitro and in vivo [39, 116]. Moreover, PKC signaling influences this key epigenetic effect by regulating phosphorylation Jun proteins [149].

DGKeta gained attention after several genome-wide association studies found DGKeta as one of the replicated risk genes in BD [150]. DGKeta is coded by DGKH gene, and polymorphisms in the DGKH gene have been observed to confer susceptibility to BD [151]. DGK risk haplotypes in humans are also associated with enlarged amygdala in BD patients [152]. Moreover, DGK is involved in biosynthesis of glycerophospholipids (GPLs) [153]. Alterations in membrane GPL composition has been implicated in several neuropsychiatric disorders, including BD [154]. DGKeta was observed to negatively regulate the PLC/PKC pathway by converting inactivating DAG, a cofactor of PKC, to phosphatidic acid [155–157], hence preventing overactivation of PKC cascade. Recently, DGKeta and PKC have been shown to reciprocally inhibit each other [158]. Specifically, in HEK 293 cells, DGKeta overexpression increased and PKC activation decreased G-protein-coupled receptor (GPCR) signaling [158]. DGKeta overexpression prevented PKC activation-induced desensitization of GPCR signaling [158]. Pharmacological activation of PKC, in turn, prevented DGKeta overexpression-induced enhanced GPCR (muscarinic and purinergic) signaling [158] (Fig. 2). In the light of significant evidence in support of PKC hyperactivity in BD, hypoactive DGKeta function can be hypothesized in BD [159]. In fact, DGKeta knockout mice

display manic features that were ameliorated by lithium [160]. In contrast, patients with BD show increased DGKeta expression [161]. Given a reciprocal regulation between DGK and PKC [162], a compensatory increase in DGK expression can be hypothesized. However, future investigations are needed to further clarify the role of DGKeta in the pathophysiology of BD [163].

PKCI/HINT1 is another gene candidate implicated in BD. PKCI/HINT1 is a haploinsufficient tumor suppressor gene [164]. In a meta-analysis, PKCI/HINT1 expression in dorsolateral PFC was found to be decreased in BD [165]. PKCI/HINT1 knockout mice do not show baseline hyperlocomotion but display enhanced locomotor response to AMPH treatment [166], increased risk-taking and antidepressant-like behavior [167], emotional arousal, and PKC expression [168]. As increased PKCI/HINT1 expression shows antineoplastic properties in colon and hepatic cells, a hypoactive PKCI/HINT1 may indicate activated neoplastic signaling that underlies BD [164].

Suicidality is a common occurrence in patients with BD, and PKC is also implicated in suicidal behavior in patients with BD [169, 170]. In a meta-analysis of 8,700 patients, both unipolar depression and BD were found to be associated with suicidality and gene locus for PKCε [170]. Moreover, using the convergent functional genomics approach, MARCKS, a PKC substrate [171], was found to be one of the 6 peripheral biomarkers that predict past and future hospitalization in relation to suicidality in patients with BD [172]. This observation further implicates hyperactive PKC signaling in the etiopathogenesis of BD.

Conclusion

An understanding of the pathogenesis of BD is needed to develop more effective therapies. Research in the past decade has identified several mechanisms such as apoptotic, neoplastic, inflammatory, energy homeostasis, synaptic neurotransmission, and oxidative balance to be involved in the pathophysiology of BD. However, PKC appears to play a central role in all these processes [173]. This attribution is supported by the effectiveness of PKC inhibitors, such as TMX and endoxifen, in treating manic symptoms in humans. Nevertheless, future research is warranted to develop safe and specific therapies for this devastating disorder.

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Disclosure Statement

The authors declare that they have not had any financial, personal or other relationships that have influenced the work.

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