Mol Neurobiol (2011) 44:407–419
DOI 10.1007/s12035-011-8210-4

A Role for the PKC Signaling System in the Pathophysiology and Treatment of Mood Disorders: Involvement of a Functional Imbalance?

Erika Abrial · Guillaume Lucas · Hélène Scarna · Nasser Haddjeri · Laura Lambás-Señas

Received: 2 August 2011 / Accepted: 20 September 2011 / Published online: 5 October 2011

Abstract Mood disorders, such as bipolar and major depressive disorders, are frequent, severe, and often disabling neuropsychiatric diseases affecting millions of individuals worldwide. Available mood stabilizers and antidepressants remain unsatisfactory because of their delayed and partial therapeutic efficacy. Therefore, the development of targeted therapies, working more rapidly and being fully effective, is urgently needed. In this context, the protein kinase C (PKC) signaling system, which regulates multiple neuronal processes implicated in mood regulation, can constitute a novel therapeutic target. This paper reviews the currently available knowledge regarding the role of the PKC signaling pathway in the pathophysiology of mood disorders and the therapeutic potential of PKC modulators. Current antidepressants and mood stabilizers have been shown to modulate the PKC pathway, and the inhibition of this intracellular signaling cascade results in antimanic-like properties in animal models. Disrupted PKC activity has been found both in postmortem brains and platelet from patients with mood disorders. Finally, the PKC inhibitor tamoxifen has recently demonstrated potent antimanic properties in several clinical trials. Overall, emerging data from preclinical and clinical research suggest an imbalance of the PKC signaling system in mood disorders. Thus, PKC may be a critical molecular target for the development of innovative therapeutics.

Keywords Depression · Mania · Protein kinase C · Mood disorders · Intracellular signaling pathways

E. Abrial (✉) · G. Lucas · H. Scarna · N. Haddjeri · L. Lambás-Señas (✉)
Laboratoire de Neuropsychopharmacologie, Université Lyon 1,
8 avenue Rockefeller,
69373 Lyon Cedex 08, France
e-mail: erika.abrial@univ-lyon1.fr
e-mail: lambas@univ-lyon1.fr

G. Lucas · H. Scarna · N. Haddjeri · L. Lambás-Señas
INSERM,
101, rue de Tolbiac,
75654 Paris Cedex 13, France

Introduction

Mood disorders including major depressive disorder (MDD) and bipolar disorder (BPD) are common, severe, and often highly disabling illnesses that afflict millions of individuals worldwide. About 16% and 1% of the general population are estimated to be affected by MDD and BPD, respectively, at least once in their lifetime [1].

MDD, also named unipolar depression, is characterized by depressed mood and loss of interest or pleasure in normal activities. The hallmarks of BPD are mood shifts between episodes of elevated (mania) and low (bipolar depression) mood. Currently, the diagnostic criteria for an episode of bipolar depression are the same as for MDD [2, 3].

Presently, the neurobiological mechanisms underlying the pathophysiology of mood disorders are not fully understood. Historically, the neuronal systems that have received the greatest attention in depression were the monoaminergic neurotransmitter ones. This was based on the initial finding that the main biological action of tricyclics and monoamine oxidase inhibitors, the first generations of effective antidepressants (ADs), consists of a potent inhibition of serotonin (5-HT), norepinephrine, and, to a lesser extent, dopamine reuptake. More recently, it became apparent that among the monoamines, 5-HT plays a crucial role in the mechanism of action of ADs, as

demonstrated by the successful use of selective serotonin reuptake inhibitors (SSRIs) since more than two decades. Indeed, it remains that the common feature of all molecules used to date, including the recently developed selective norepinephrine or dual (mixed) reuptake inhibitors, is their ability to increase central 5-HT neurotransmission [4, 5]. With regard to BPD, several neurotransmitters, including monoamines, acetylcholine, and amino acids, are likely to be involved in the pathophysiology of this disease [6–8]. Accordingly, either various BPD medications (atypical antipsychotics, benzodiazepines) or drugs precipitating mood switches (amphetamine, physostigmine) act through these neurotransmitter systems. Yet, the cellular targets of lithium, the gold standard treatment of BPD since the 1950s, and valproate and carbamazepine, two other commonly prescribed mood stabilizers, are still largely unknown.

Besides, it is now believed that mood disorders may be associated with impairments of structural plasticity and neuronal resilience and that current treatments may act by correcting this dysfunction. In support of this hypothesis, different forms of chronic stress have been shown to reduce adult neurogenesis in the rodent hippocampus, and this deficit was reversed by chronic AD treatment [9, 10]. In addition, neuroimaging studies in patients with mood disorders have demonstrated selective structure and function abnormalities across brain areas involved in processing motivation and emotional behaviors, such as prefrontal cortex and limbic regions [11].

Thus far, although marked improvements in the safety profile of drug therapies for mood disorders have been achieved, there are still a number of critical dimensions for which improvements are needed. One important, if not critical, dimension consists of effectiveness. In MDD for instance, only one third of patients fully respond to conventional AD treatments, one third are partial responders and undergo polytherapies (i.e., combined treatments of several ADs or AD and other medication), and the remaining one third does not respond to any mono- or polytherapy. In addition, the full efficacy of classic ADs on mood improvement requires at least 3 to 4 weeks of treatment. This delayed onset of action has been suggested to be linked to the late desensitization of inhibitory 5-HT_{1A} autoreceptors that occurs few weeks after the beginning of the treatment, concomitantly with the improvement in mood [4, 12]. The situation is similarly sobering for BPD, where a sizable proportion of patients fail to respond to currently available therapeutics. The presence of unwanted side effects may also limit adherence to treatment in subjects with mood disorders. There is consequently a critical, unmet need to both identify and test novel drug targets for mood disorders in order to develop new treatments more effective and more rapidly acting than currently available medications.

Recently, new strategies of research have emerged, in order to shorten the onset of action of ADs by "bypassing" the 5-HT-related inertia. They were oriented toward investigating beyond the receptor level, searching for the intracellular targets that were affected by AD treatment. In parallel, recent studies have shown that lithium and valproate, two structurally dissimilar mood stabilizers, targeted several intracellular signaling pathways, such as glycogen synthase kinase-3 (GSK-3) or protein kinase C (PKC) [13].

Intracellular signaling cascades may be the common denominator of all the assumptions on pathophysiological mechanisms made so far, by transducing a wide range of signals coming from multiple receptors of neurotransmitters and neurotrophic factors, which have been implicated in mood disorders. Targeting such signaling pathways might thus exert global and more potent effects.

This article reviews the findings implicating the PKC signaling pathway in the pathophysiology and treatment of mood disorders and points out this intracellular signaling molecule as a promising target for the development of novel therapeutics for these debilitating diseases.

The PKC Signaling Pathway

The "PKC" term actually defines a family of serine/threonine kinases, which are involved in the signal transduction mechanisms of tyrosine kinase and G protein-coupled receptors. The family comprises 10 different [...] 9 genes in mammals. All PKCs consist of C-terminal catalytic and N-terminal regulatory domains. The catalytic region is highly homologous among different isoforms. By contrast, the regulatory region, which is responsible for the second messenger requirements of the isozymes, differs among PKCs. The PKC family is thus divided into three classes depending on their structure and requirements for activation: (1) *conventional PKCs*, composed of PKCα, PKCβI, PKCβII, and PKCγ, require both Ca^{2+} and diacylglycerol (DAG) for activation; (2) *novel PKCs*, which include PKCδ, PKCε, PKCη, and PKCθ, are also activated by DAG but not by Ca^{2+}; and (3) *atypical PKCs*, consisting of ι/λ and ζ, require neither Ca^{2+} nor DAG to be activated [14].

All PKC isozymes are highly expressed in the central nervous system. Particularly, the ε isoform is predominantly expressed in the brain compared to the other tissues, and the PKCγ is exclusively localized in the brain [15]. A large majority of PKC isozymes is highly expressed in brain regions involved in mood regulation (i.e., hippocampus, frontal cortex), both within neurons and glia [15–17].

The mechanisms leading to the activation of conventional PKC isoforms have been extensively studied and are schematized in Fig. 1. Upon stimulation of receptors that increase intracellular Ca^{2+} and DAG, PKC is recruited to

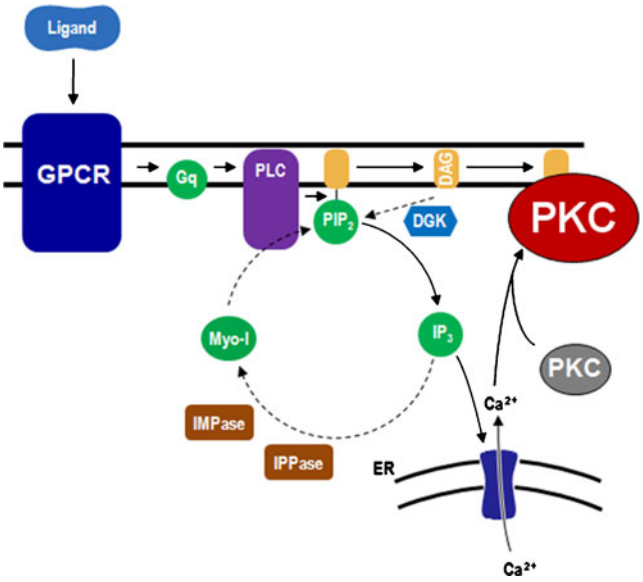

Fig. 1 Activation of conventional PKC isoforms. The interaction of an agonist ligand with G-protein coupled receptor activates a Gq protein. The Gq protein activates the phospholipase C (PLC), which in turn cleaves the phosphatidylinositol-4,5-bisphosphate (PIP_2) into DAG and inositol-1,4,5-trisphosphate (IP_3). IP_3 interacts with calcium channels on the endoplasmic reticulum, to release Ca^{2+} from intracellular stores to cytoplasm. Increase of intracellular Ca^{2+} then facilitates the translocation of PKC to the cell membrane, where it is activated by DAG. Recycling of IP_3 is carried out through the phosphoinositide cycle, in which two enzymes, inositol polyphosphate-1-phosphatase (IPPase) and inositol monophosphatase (IMPase), play a key role. DAG is converted into PIP_2 through a series of metabolic steps that involves the action of an enzyme called DAG kinase (DGK). *ER* endoplasmic reticulum, *Myo-I* myo-inositol

the cell membrane and undergoes conformational changes, allowing substrate binding and phosphorylation. Figure 2 summarizes the major substrates of PKC that have been described in the literature [18–28]. Through their phosphorylation, PKC is able to modulate a multiplicity of neuronal functions such as short- (neurotransmitter release and ion fluxes), mid- (receptor regulation), and long-term processes (cell proliferation, synaptic remodeling, and gene expression). Interestingly, three major substrates, myristoylated alanine-rich C kinase substrate (MARCKS), GAP-43, and neurogranin are involved in the pre- and postsynaptic regulation of neurotransmitter release and synaptic plasticity [18, 27].

Actually, PKC plays a major role in synaptic cross-talk and transduces converging postsynaptic signals generated after external stimulation of cells via several Gq protein-coupled receptors—including serotonin ($5\text{-}HT_2$), norepinephrine (α_1), acetylcholine (M_1, M_3, and M_5), and glutamate (mGluR1 and mGluR5) receptors—and through the receptor TrkB, activated by neurotrophic factors such as neurotrophin-3/4 and brain-derived neurotrophic factor. Thus, PKC is at the crossroads of transduction pathways from a wide variety of neurotransmitters and growth factors, which are likely implicated in mood disorders.

The activity of PKC can be pharmacologically modulated by exogenous compounds. Thus, many PKC inhibitors have been designed, but it appears that the vast majority of them address in fact multiple molecular targets. These inhibitors act

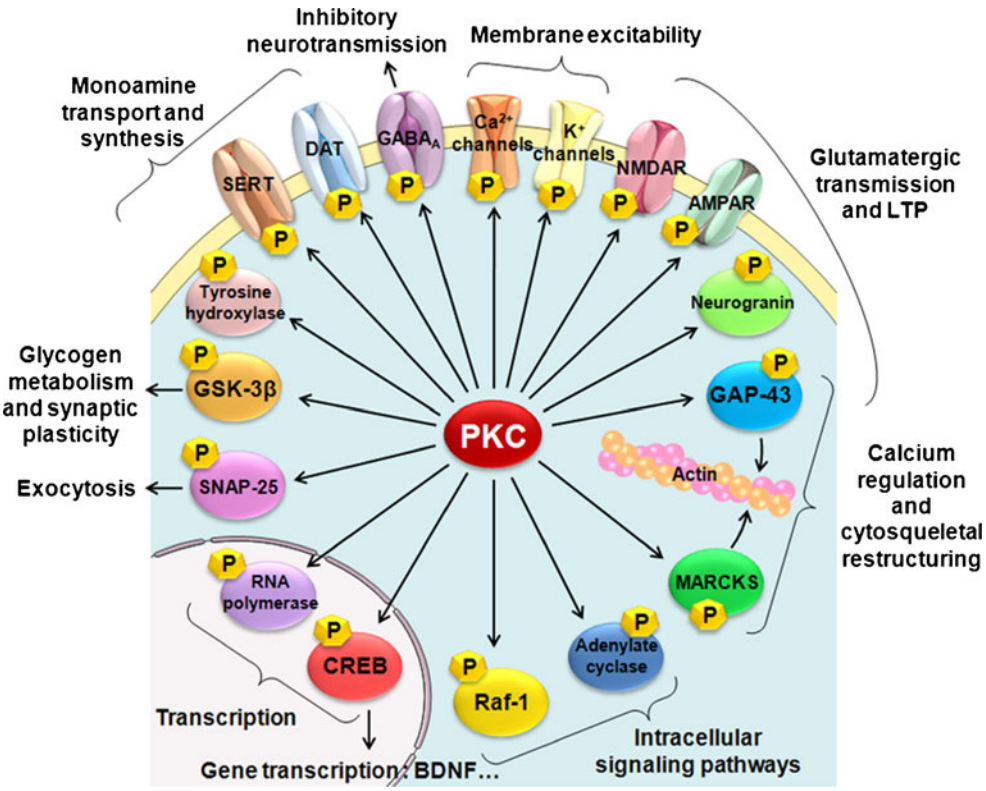

Fig. 2 Schematic illustration of main PKC substrates in the central nervous system, and functions related to mood regulation. Activated PKC phosphorylates multiple substrate proteins and thereby affects gene expression, synaptic plasticity, and neurotransmission, which in turn regulate mood-related behaviors. *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *CREB* cAMP regulatory element-binding protein, *DAT* dopamine transporter, *$GABA_A$* γ-aminobutyric acid A receptor, *GAP-43* growth-associated protein-43, *GSK-3β* glycogen synthase kinase 3β, *LTP* long-term potentiation, *MARCKS* myristoylated alanine-rich C kinase substrate, *NMDAR* N-methyl-D-aspartate receptor, *SERT* serotonin transporter

either at the regulatory (NPC-15437, tamoxifen, and calphostin C) or at the catalytic domain (Ro31-8220, chelerythrine, and H-7) of PKC. Among the cited inhibitors, only chelerythrine, NPC-15437, and calphostin C are selective of the PKC (for review, see [29]). In addition to their anti-PKC properties, tamoxifen is also an estrogen receptor modulator, and the other molecules inhibit several other kinases. Conversely, PKC activators have been far less developed. Most are phorbol esters, and in addition to not being specific to PKC, they are also potent tumor promoters [30, 31]. In spite of limitations exhibited by PKC modulators, they have been extensively used to elucidate the physiological functions of this family of kinases. So far, none of the identified PKC modulators display selectivity toward a particular isozyme. Another generation of more selective PKC modulators would therefore be highly useful in defining the role of each PKC isozyme.

Preclinical Studies

Is the PKC Pathway Influenced by Mood Disorder Treatments?

With the purpose of developing improved therapeutics, a significant proportion of the recently conducted research in the field has been devoted to identify common targets, shared by the different existing medications. In this context, it appears of interest to assess the extent to which the PKC system can be modulated by current mood stabilizers (lithium, and the antiepileptics valproate and carbamazepine) and antimanic agents (atypical antipsychotics), as well as by ADs (notably SSRIs).

Mood Stabilizers and Antimanic Agents Several investigations have revealed that the prototypical mood stabilizer lithium inhibits PKC function. Thus, Bitran et al. [32] showed an attenuation of PKC activity after a prolonged in vitro exposure of HL60 cells to lithium. This effect could be related to an action on α and ε isoforms, since a decrease of the levels of these isoforms was observed following incubation with lithium [32, 33]. This apparent selectivity of lithium towards PKCα and PKCε isozymes was subsequently confirmed in vivo by the same group. Thus, chronic (5 weeks), but not subacute (5 days), treatment of rats with lithium decreased the levels of membrane-associated PKCα and PKCε in both the hippocampus and frontal cortex, without changing those of the PKCβI, PKCβII, PKCγ, PKCδ, or PKCζ isoforms [33]. This result is congruent with the diminution of rat hippocampal PKC activity observed after 5 weeks of lithium treatment [34]. This delayed decrease in PKC function is clinically relevant since lithium's efficacy appears after a comparable time frame in the treatment of BPD. Additionally, chronic administration of lithium also decreased the phosphorylation of several PKC substrates, such as MARCKS, neurogranin, NMDA, and AMPA receptors in rodent hippocampus and cortex [35–37]. All these data suggest that PKC could be involved in the therapeutic effect of lithium.

Similarly, despite being structurally dissimilar to lithium, valproate and carbamazepine share most of the effects of lithium on PKC. Like lithium, chronic carbamazepine administration decreased PKC-mediated phosphorylation of several endogenous substrates within the rat brain [35]. Chronic valproate reduced the activity of PKC, both in vitro [33, 38] and in vivo [33]. Importantly, valproate also induced an isozyme-selective decrease in the levels of PKCα and PKCε, but not PKCδ and PKCζ in C6 glioma cells [38], as well as a decrease in cortical PKCα levels in chronically treated rats [33]. Finally, even atypical antipsychotics, used for the treatment of acute mania, seem to modulate the PKC pathway. Clozapine for instance, decreased PKC activity after 5 days of exposure in mouse neuroblastoma cells [39].

These data demonstrate that mood-stabilizing agents from different classes have a common inhibitory effect on PKC and support that this intracellular pathway could contribute, at least in part, to their therapeutic effect. Nevertheless, it is important to note that there is no current evidence that these agents target PKC in a direct manner. Instead, they may rather target upstream effectors, such as the phosphoinositide cycle. Indeed, lithium directly inhibits IPPase and IMPase and therefore limits the IP_3 recycling into PIP_2, thus attenuating intracellular calcium release and PKC activation (Fig. 1). Interestingly, a magnetic resonance spectroscopy study showed that lithium rapidly reduced myo-inositol levels in the frontal cortex of bipolar patients within 5–7 days, whereas symptom improvement did not occur before 3 to 4 weeks [40]. This time lag between myo-inositol lowering and clinical amelioration suggests that the reduction of myo-inositol per se does not underlie lithium's therapeutic effects. However, this event may initiate a cascade of secondary signaling in which downstream effectors, like PKC, could be ultimately responsible for lithium's therapeutic efficacy.

Antidepressant Treatments A small number of studies have examined the effect of chronic treatment of ADs on the PKC pathway and have yield mixed results. Indeed, increased PKC activity and MARCKS phosphorylation have been reported in the rat prefrontal cortex after a 10-day treatment with the tricyclic AD imipramine [37]. However, it was also shown that chronic administration (3 weeks) of fluoxetine or desipramine decreased PKC activity in the rat

cortex and hippocampus, while a single dose of either AD failed to induce any PKC activity changes in both of these structures [41]. In particular, it appears that PKCγ and PKCδ are the most affected isoforms since chronic (3 weeks) AD treatment with the SSRIs fluoxetine or citalopram selectively reduced expression of PKCγ and PKCδ in the rat whole brain [42].

Beyond pharmacological therapies for mood disorders, it is interesting to note that electroconvulsive seizures, an efficient alternative to severe AD-refractory depressions, increased the phosphorylation of PKC substrates, namely GAP-43, MARCKS, and neurogranin in the rat frontal cortex and hippocampus [43].

Behavioral Effects of PKC Modulators on Animal Models of Mania and Depression

Manic-Like Behaviors There is currently no animal model available relevant enough to reproduce all the symptoms of BPD, and in particular, the alternation of depressive and manic states—a core feature of the disease. Instead, these animal models mimic only some of the symptoms of the manic state [44].

One of the most established behavioral rodent model of mania is based on the measurement of psychostimulant-induced hyperactivity, a behavior that is reproducibly attenuated by a number of treatments used in mania, including lithium, valproate, and antipsychotics [45, 46]. Studies performed in this model have suggested that PKC could be involved in the modulation of manic-like behavior. Thus, the two PKC inhibitors tamoxifen and chelerythrine attenuated the hyperlocomotion induced by amphetamine in mice and rats [47–49]. Two other PKC inhibitors, H-7 and Ro31-8220, administered respectively in the ventral tegmental area or in the nucleus accumbens, also reduced psychostimulant-induced hyperactivity [50, 51]. This effect of PKC inhibitors could be, at least in part, dopamine-dependent, because it is known that PKC regulates psychostimulant-mediated dopamine release probably via the regulation of dopamine transporter activity [52, 53]. A recent study showing that PKCβ knockout (KO) mice exhibited impaired locomotor responsiveness to amphetamine provided evidence that the β isoform may be more specifically included in this regulation [54]. Interestingly, Szabo et al. [37] revealed that chronic treatment with amphetamine increased membrane and cytosolic PKC activity and phosphorylation of its main cellular substrates, MARCKS and neurogranin, in the rat frontal cortex. Similarly, these authors also demonstrated an enhancement of MARCKS and neurogranin phosphorylation in the frontal cortex after sleep deprivation, another putative animal model of mania [55].

Increased hedonistic drive and increased tendency to drug abuse are well-known facets of manic behavior. These behaviors can be modeled by using the consumption of reward and conditioned place preference (CPP) paradigms [56]. Interestingly, selective (NPC-15437, chelerythrine, calphostin C) and non-selective (H-7) PKC inhibitors, regardless of the brain region in which they are injected (amygdala, nucleus accumbens, or more widely in the lateral ventricle), diminished the CPP induced by several drugs of abuse (morphine, cocaine, or methamphetamine) [57–60]. Targeted genetic deletions also support the involvement of PKC in such affective-like behaviors. Thus, PKCγ KO mice showed reduced morphine-induced CPP [60] and PKCε KO mice exhibited reduced ethanol self-administration [61].

Augmentation of risk-taking behaviors may be interpreted as another facet of mania, and it can be assessed in anxiety-related protocols [56]. In this concern, there is recent evidence suggesting that PKC inhibition decreases risk-taking behaviors. Indeed, we recently showed that tamoxifen or chelerythrine increased the avoidance of anxiogenic zones in the elevated plus-maze or the bright-lighted open field [62].

In addition, using the resident-intruder aggression test, Raygada et al. [63] reported that mice exposed in utero to the PKC activators n-6 polyunsaturated fatty acids subsequently developed aggressiveness. These results support the claim that PKC activation can induce manic-like behaviors.

Finally, activation of PKC in the prefrontal cortex with phorbol esters has been shown to induce cognitive deficits in monkeys and rodents [64]. Interestingly, it was also shown that inhibition of PKC rescued working memory impairments [65]. These findings are highly relevant to mania, as disrupted cognitive function constitutes a major symptom of bipolar illness.

Overall, behavioral data from animal models of mania support the notion that PKC inhibition may have antimanic properties, whereas PKC activation might induce manic-like behaviors.

Depression-Like Behaviors Alterations of the PKC signaling pathway have been found in various animal models of depression, and more generally after stress. Thus, it was recently shown that C57Bl/6 mice, exposed to chronic mild stress, displayed decreased hippocampal PKC activity [66]. Besides, Park et al. [67] showed that a chronic mild stress protocol reduced the expression of the PKC substrate GAP-43 mRNA in the rat dentate gyrus. In the olfactory bulbectomy paradigm, a significant decrease of both the PKCα autophosphorylation and the phosphorylation of the NMDA receptor subunit NR1 on its PKC-dependent site (Ser 896) was observed in the CA1 region of the hippocampus [68, 69]. Likewise, in the learned helplessness

rat model, repeated inescapable shock significantly attenuated PLC activity and PLCγ_1 and PLCβ_1 protein and mRNA levels, both in the frontal cortex and hippocampus [70]. Moreover, PKCβI expression and translocation were reduced in the hippocampus of adult rats exposed to prenatal stress [71]. In other chronic stress paradigms, namely restrained stress and rats subjected to 4 weeks of forced swimming, decreases of hippocampal PKCα mRNA expression or PKC activity were found [72, 73].

Given that decreases in PKC function have been found in several animal models of depression and chronic stress, it appears likely that pharmacological activation of the PKC pathway may exert antidepressant-like effects. Accordingly, in two screening tests for ADs (forced swim and open space swim tests), acute administration of the PKC activators phorbol 12-myristate 13-acetate (PMA) or bryostatin-1 in naive rats resulted in an antidepressant-like activity, as indicated by a reduction of immobility. Further, these effects were strongly reversed by co-administration of a PKC inhibitor [74, 75]. In addition, we recently showed that a chronic treatment with the PKC inhibitors tamoxifen and chelerythrine increased the immobility behavior of naive rats in the forced swim test [62]. Moreover, the offspring of dams exposed to the PKC activators n-6 polyunsaturated fatty acids spent less time immobile in the forced swim test at adulthood [63]. All these findings support the assumption that PKC activation can produce an antidepressant-like effect. Further investigations on the behavioral effects of PKC modulators in animal models of depression are needed to comfort this hypothesis. From a therapeutic point of view, it is expected that new, more selective, and effective activators will be developed in the next future. Unfortunately indeed, PMA has potent tumorigenic effects, and both PMA and bryostatin-1 rapidly downregulate PKC translocation to the membrane, thus causing PKC inhibition at high doses and/or prolonged exposure.

The above preclinical findings are in favor of a PKC system failure as one of the possible causes of mood disorders. More precisely, it can be postulated that this intracellular pathway is overactive in mania and weakened in depression.

Clinical Studies

Abnormalities of the PKC System in Patients with Mood Disorders

Genetic Studies Mood disorders, like most psychiatric disorders, have complex causes that likely involve genetic factors in addition to non-genetic influences. MDD and BPD appear to be polygenic diseases in which several genes, each with a modest influence on its own, contribute to the risk of developing such diseases.

Most of the genetic correlation studies associating mood disorders with the PKC signaling pathway have focused attention on BPD. To date, there is no clear evidence of a direct link between specific genes of the PKC pathway proteins and mood disorders. However, some polymorphisms of upstream effectors have been associated with BPD. Thus, two independent genome-wide association studies have identified the DAG kinase η gene as a risk factor for bipolar disorder [76, 77]. DAG kinase constitutes a key protein of the PKC pathway, regulating PKC activation by recycling the endogenous PKC activator DAG back to PIP_2 (Fig. 1). Moreover, it was found that bipolar patients who were considered excellent responders to lithium prophylaxis had a higher frequency of a polymorphism of the gene coding for PLCγ_1, compared with the control group [78]. Besides, apparent associations were found between inositol-monophosphatase 2 gene polymorphism and BPD [79, 80]. The inositol-monophosphatase is a critical enzyme of the inositol recycling cycle (Fig. 1) and also one of the cellular targets of lithium.

Postmortem Studies If the PKC pathway is involved in the pathophysiology of mood disorders, it might be expected that PKC, and/or other components of its pathway, would be modified in patients suffering from these diseases. Data from postmortem studies could thus be useful to identify possible dysfunctions of the PKC pathway in mood disorders.

A limited number of studies have quantified the activity and/or the expression of PKC, as well as those of upstream and downstream proteins (respectively, PLC and MARCKS) in brain tissue from patients with mood disorders. These results are summarized in Table 1. It should be noted that many factors, such as age, ante-mortem medication, substance abuse history, postmortem delay, and also the cause of death, vary widely between these studies. Moreover, the observations are mostly done in small-sized samples that include, for some of them, other mental illnesses such as in adjustment disorder, attention-deficit hyperactivity disorder, or schizophrenia [81, 82]. Therefore, achieving a thorough comparison of these studies revealed hardly feasible. Nevertheless, several abnormalities appeared to be common among postmortem tissues extracted from patients with various mood disorders. Thus, PKC activity and the levels of selected PKC isoforms were found increased in the frontal cortex of bipolar patients compared to healthy controls [83]. Regarding PLC, measures in bipolar patients reported either no effect on PLC cortical activity [84] or increased PLCβ_1 levels in the occipital cortex [85]. These postmortem data

Table 1 Postmortem brain studies in mood disorders

Diagnosis	Brain structure	Parameter assessed		Fraction	Ref.
BPD	Occipital cortex (Ba 17)	PLC activity	=	M	1
	Prefrontal cortex (Ba 10)		=	M	
	Temporal cortex (Ba 21)		=	M	
BPD	Occipital cortex (Ba17)	$PLC\beta_1$ (WB)[a]	↑	M	2
	Prefrontal cortex (Ba10)		=	M	
	Temporal cortex (Ba21)		=	M	
BPD	Frontal cortex	PKC activity	↑	M	3
		PKCγ and PKCζ (WB)	↑	M	
		PKCα (WB)	↑	M	
		PKCε (WB)	↓	M	
		PKCβ and PKCδ (WB)	=	M,C	
MDD	Prefrontal cortex (Ba 10)	PKCβI and PKCε (WB)	↓	n/a	4
		PKCβII, PKCγ, and PKCδ (WB)	=	n/a	
Suicide victims (MDD)	Prefrontal cortex (Ba8/9, Ba10)	PKCα (WB)	=	M	5
		PLCβ (WB)	=	M	
		PLC activity	=	M	
Suicide victims (MDD)	Prefrontal cortex (Ba 8/9) and Hippocampus	MARCKS phosphorylation	↓	M	6
		MARCKS (WB)	↑	M	
	Prefrontal cortex (Ba 8/9)	MARCKS mRNA	=	–	
Suicide victims (MDD and other depressions)	Prefrontal cortex (Ba 10)	PKC[b]	↑	C	7
	Hippocampus		=	M,C	
Suicide victims (7 MDD, 2 BPD in depressive state, 1 other depression)	Prefrontal cortex (Ba 9, Ba10)	PKCα, PKCβ, PKCγ, and PKCε (WB)	=	M	8
Suicide victims (incl. 3 MDD)	Prefrontal cortex (Ba 8 & 9)	PKC[b]	↓	M,C	9
Suicide victims (incl. 4 MDD)	Prefrontal cortex (Ba 9) and Hippocampus	PKC activity	↓	M,C	10
		PKCα, PKCβI, PKCβII, and PKCγ (WB)	↓	M,C	
		PKCα, PKCβ, PKCγ mRNA	↓	–	

An increased PKC activity and/or protein levels in the membrane fraction is often interpreted as an enhancement of PKC translocation/activation. *BPD* bipolar disorder, *MDD* major depressive disorder, *Ba* Brodmann area, *M* membrane fraction, *C* cytosol fraction, *1* [84], *2* [85], *3* [83], *4* [86], *5* [107], *6* [87], *7* [108], *8* [109], *9* [81], *10* [82]

[a] Protein levels assessment by western blot (WB)

[b] PKC binding assessment by [^{3}H]PDBu binding

suggest a possible overactivation of the PLC–PKC axis in discrete cortical regions. A larger number of studies have investigated the abnormalities of the PKC pathway in postmortem brains of depressive subjects. In most of them, PKC activity, expression, and levels of different isozymes were found decreased in key areas involved in mood regulation such as the prefrontal cortex and the hippocampus [81, 82, 86]. In addition, the phosphorylation of MARCKS, a major substrate of PKC, was significantly reduced in these regions [87], suggesting also that PKC activity is decreased in depressive patients. Besides, these authors also found an increase in membrane-bound MARCKS, which can also be interpreted as a decreased PKC activity, since MARCKS's phosphorylation induces its own translocation from the membrane to the cytosol [88].

In summary, postmortem studies provided some evidence of a possible upregulation of PKC function in BPD and conversely a downregulation in MDD.

Platelet Studies Blood platelets are easily accessible for study and therefore have been used as a peripheral model to study the PKC system in psychiatric patients. At difference with postmortem brain studies, for which there is an important lack of control over the actual state of the patient mood (manic, depressive, or mixed), platelet studies permitted to determine whether PKC alteration is an inherent characteristic of the disease or depends on the mood state. Additionally, these studies offer the possibility to follow the mood changes of the patient longitudinally, before and after the treatment, and thus to investigate whether the improvement of

mood after the treatment is correlated with changes of PKC activity.

When focusing only on studies performed on bipolar subjects in manic state (Table 2), it appears that the membrane-associated PKC activity is significantly increased in blood platelets [89–91]. It seems also relatively clear that treating mania with a mood stabilizer can reverse the enhancement of platelet PKC activity along with improving the mood in the same patients [90, 91]. However, data become more discrepant when different mood states are mixed in the same BPD group (manic, mixed, and depressed states) [92–94]. Regarding MDD, two out of three studies reported no change in PKC activity, neither in the membrane nor in the cytosolic fractions [89, 94].

Thus, the available evidence from platelet studies performed in patients with BPD support the hypothesis that PKC activity is increased in mania and that mood stabilizers could exert their clinical actions by counteracting this hyperactivation. However, to clearly establish that changes in PKC function are related to the state (manic or depressive) instead of the trait (major depressive versus bipolar disorders), it would be required to determine in further studies whether the PKC is inhibited in bipolar patients during the depressive phase.

An important issue was raised by these investigations with regard the extent to which changes measured in platelets actually reflect those occurring in the brain. A study therefore examined the relationship between platelet

Table 2 Platelet studies in mood disorders

Diagnosis	Treatment	Parameter assessed		Fraction	Ref.
BPD-manic state	Lithium- and antidepressant-free (≥1 week)	PKC activity	↑	M	1
BPD-manic state	n/a	PKC activity	↑	M	2
	1–2 weeks of Lithium	PKC activity	↓[c]	M, C	
BPD-manic state	Medication-free (≥2 weeks)	PKC activity	↑	M	3
	2 weeks of lithium or valproate	PKC activity	↓[c]	M, C	
BPD-manic or mixed state	Medication-free (≥1 week)	PKC activity	↓	M, C	4
		PKCβI and βII (WB)[a]	↓	M, C	
		PKCα and PKCδ (WB)	=	M, C	
	8 weeks of mood stabilizer or antipsychotic therapy	PKC activity	↑[c]	M, C	
		PKCα, PKCβI, PKCβII, and PKCδ (WB)	=[c]	M, C	
BPD-euthymic state	Lithium-treated (<6 months)	PKCα (WB)	=	M, C	5
BPD-euthymic state	Lithium-treated (<1 month)	PKCα (WB)	↓	C	6
		PKCβI, PKCβII, PKCδ, and PKCε (WB)	=	M, C	
		PIP_2 (WB)	↓	M	
BPD (10 depressive, 4 manic states)	Lithium-free (>1 year)	PKCα (WB)	=	M, C	5
BPD (6 manic, 5 depressive and 4 mixed states)	Medication-free (≥2 weeks)	PKC activity	↓	M, C	7
		PKCα, PKCβI, PKCβII (WB)	↓	M, C	
		PKCδ (WB)	=	M, C	
		MARCKS (WB)	↑	M, C	
		PLC activity	↓	M, C	
MDD	Medication-free (≥2 weeks)	PKC[b]	↑	C	8
MDD	Lithium- and antidepressant-free (≥1 week)	PKC activity	=	M, C	1
MDD	Medication-free (≥2 weeks)	PKC activity	=	M, C	7
		PKCα, PKCβI, PKCβII (WB)	=	M, C	
		PKCδ (WB)	=	M, C	
		MARCKS (WB)	=	M, C	
		PLC activity	=	M, C	

An increased PKC activity and/or protein levels in the membrane fraction is often interpreted as an enhancement of PKC translocation/activation

BPD bipolar disorder, *MDD* major depressive disorder, *M* membrane fraction, *C* cytosol fraction, *1* [89], *2* [90], *3* [91], *4* [92], *5* [93], *6* [110], *7* [94], *8* [111]

[a] Protein levels assessment by western blot (WB)

[b] PKC binding assessment by [^{3}H]PDBu binding

All differences are expressed versus healthy controls, except for [c] versus patients before treatment

and brain PKC in rats and demonstrated that chronic treatment with lithium reduced the levels of PKCα, both in platelets and in the frontal cortex [33]. Moreover, the authors found a strong correlation between platelet and frontal cortex PKCα measures. However, some PKC isozymes found in the central nervous system are not expressed in platelets, as for the PKC δ and PKC ε [89]. Caution will be warranted when interpreting the PKC data obtained from platelets.

Therapeutic Relevance of Targeting PKC in Mood Disorders: First Clinical Trials

To date, five clinical studies have demonstrated the effectiveness of the PKC inhibitor tamoxifen in the treatment of acute mania in bipolar patients. Given either alone [95], as an adjunctive treatment to lithium [96, 97], or in lorazepam-treated patients [98, 99], tamoxifen resulted in a significant antimanic effect, stronger than that of lithium [96, 100]. Rates of response, determined as the percentage of patients with 50% reduction in Young Mania Rating Scale (YMRS) score from baseline to trial completion, varied from 48% to 95%. In the study by Zarate et al. [99], daily YMRS ratings were obtained during the first week of treatment, thus permitting the assessment of early antimanic effect. Subjects on tamoxifen showed significant improvement in mania compared to placebo as early as 5 days, an effect that remained significant throughout the 3-week trial.

Tamoxifen, the most widely used agent for hormonal therapy of breast cancer, is a synthetic selective estrogen receptor modulator (SERM) that inhibits PKC by acting directly on the regulatory domain of PKCα, PKCβI, PKCη, PKCδ, and PKCζ [101]. Accordingly, it can be suggested that tamoxifen pharmacological action on both estrogen receptors and PKC could contribute to its antimanic reported effects. In this concern, Kulkarni et al. [97] showed a better improvement of manic symptoms in bipolar patients treated with tamoxifen than those treated with the anti-estrogen medroxyprogesterone. Moreover, in a preliminary clinical investigation, Mallinger et al. [102] highlighted that verapamil, a calcium channel blocker which also has PKC inhibitory activity, had no effect when given as monotherapy but demonstrated antimanic efficacy when combined with lithium in lithium-refractory patients, suggesting that the antimanic effect may be mediated by additive actions of the two agents on the PKC pathway. These clinical data reinforce the relevance of targeting PKC for the treatment of mania.

One of the strengths of tamoxifen is that, compared to lithium, it causes relatively few side effects. Indeed, lithium can cause hand tremor, polydipsia, polyuria, and a decrease of thyroid function. Ingested at high doses, lithium poisoning produces renal failure and convulsions and can also cause coma [103]. Tamoxifen is fairly tolerated even at high doses (up to 200 mg/day) [104], and its side effects are the same as the other SERMs used in breast cancer (toremifene, raloxifene): nausea, hot flashes, and tiredness. This highlights that targeting a ubiquitous molecule does not necessarily induce dramatic side effects. However, although being effective and safe for "short-term" treatment of mania, its long-term efficacy and role in the maintenance treatment of BPD remains to be determined. In all cases, the above clinical studies raise the need to develop brain-penetrant selective PKC blockers with no side effects related to estrogen receptor modulation.

These promising results of tamoxifen on mania lead to address the issue of a potential interest of PKC modulation in the treatment of depression. Although no clinical study has yet been expressly conducted to evaluate the effects of

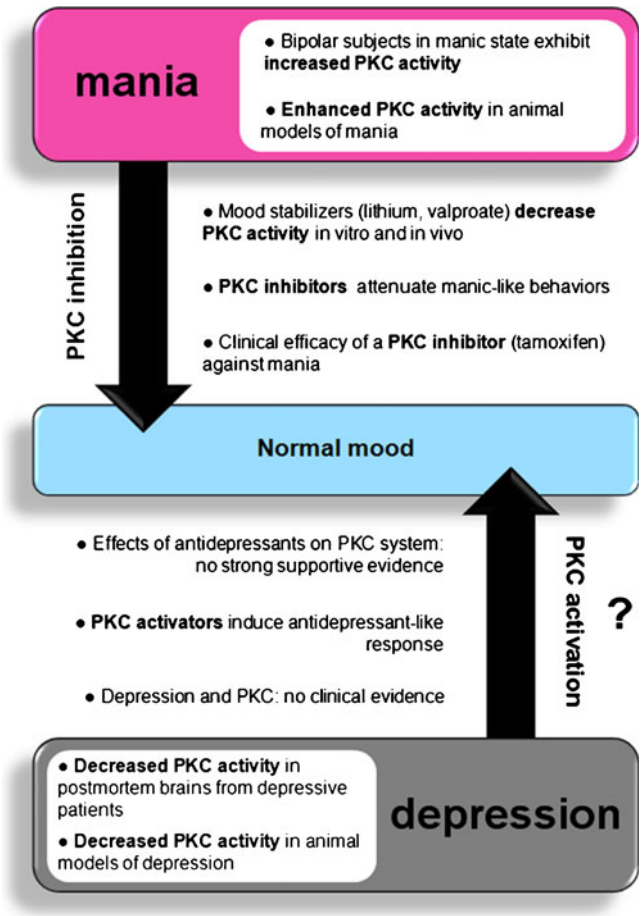

Fig. 3 Involvement of the PKC signaling system in the pathophysiology and treatment of mood disorders. Data from preclinical and clinical studies support the hypothesis of a functional imbalance of the PKC signaling system in mood disorders. This pathway may be upregulated in mania, and consequently the inhibition of PKC would reverse the mood elevation. Conversely, there are emerging preclinical data indicating a downregulation of the PKC system in depression. The potential use of PKC activators as antidepressants needs to be further evaluated

tamoxifen in depressed patients, the relationship between tamoxifen and depression has already been examined in breast cancer patients and has yielded mixed results. Indeed, in some trials and case reports, a subset of patients has discontinued tamoxifen therapy because of mild to moderate depressive symptoms [105]. These data are, however, difficult to interpret, mostly by the fact that breast cancer by itself can increase the incidence of depression compared to patients without the disease. Nevertheless, a question that future clinical studies should focus on is whether a PKC inhibitor, efficient in treating mania, may trigger a mood switch from mania to depression. Four out of the five clinical studies on tamoxifen and bipolar mania have already started to answer that issue and showed that tamoxifen was without any significant effect on depression scores, at least for the period investigated [95, 96, 98, 99].

Conclusion and Perspectives: Do PKC Modulators Have a Future in the Treatment of Mood Disorders?

Together, the preclinical and clinical data from the literature unveil a possible imbalance of the PKC signaling system in mood disorders. In Fig. 3, we summarize several key points supporting the hypothesis of a hyperactivity of the PKC system in mania and a hypoactivity in depression. Inhibition of PKC can thus be an interesting strategy for the treatment of manic episodes, as several clinical trials have already demonstrated since a few years. Conversely, and although it has been much less studied so far, PKC activators might be used in the future as the first intracellular-targeting ADs. The finding that a single intracellular signaling system may be involved in *both mood states* is of primary importance for the understanding of molecular mechanisms implicated in the pathophysiology of BPD. The heterogeneity of PKC isoforms raises the possibility that each isozyme may have its own activation pattern, depending on the mood state. If so, it cannot be excluded that distinct isozymes could be selectively involved in either mania or depression. The increasing knowledge of the role of each of the isoforms in mood disorders will certainly lead, in the next decade, to the major challenge of designing novel isozyme-targeted PKC modulators as it is already the case for the PKCε-selective activator DCP-LA [106].

References

1. Kessler RC, Chiu WT, Demler O, Walters EE (2005) Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:617–627. doi:10.1001/archpsyc.62.6.617
2. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders (Revised 4th edn). American Psychiatric Association, Washington, DC
3. Frye MA (2011) Clinical practice. Bipolar disorder–a focus on depression. N Engl J Med 364:51–59. doi:10.1056/NEJMcp1000402
4. Blier P, de Montigny C (1999) Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. Neuropsychopharmacology 21:91S–98S. doi:10.1016/S0893-133X(99)00036-6
5. Faure C, Mnie-Filali O, Haddjeri N (2006) Long-term adaptive changes induced by serotonergic antidepressant drugs. Expert Rev Neurother 6:235–245. doi:10.1586/14737175.6.2.235
6. Chen J, Fang Y, Kemp DE et al (2010) Switching to hypomania and mania: differential neurochemical, neuropsychological, and pharmacologic triggers and their mechanisms. Curr Psychiatry Rep 12:512–521. doi:10.1007/s11920-010-0157-z
7. Rapoport SI, Basselin M, Kim H-W, Rao JS (2009) Bipolar disorder and mechanisms of action of mood stabilizers. Brain Res Rev 61:185–209. doi:10.1016/j.brainresrev.2009.06.003
8. Zarate C, Machado-Vieira R, Henter I et al (2010) Glutamatergic modulators: the future of treating mood disorders? Harv Rev Psychiatry 18:293–303. doi:10.3109/10673229.2010.511059
9. Castrén E (2005) Is mood chemistry? Nat Rev Neurosci 6:241–246. doi:10.1sj.npp./nrn1629
10. Pittenger C, Duman RS (2008) Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33:88–109. doi:10.1sj.npp./sj.npp.1301574
11. Drevets WC (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11:240–249. doi:10.1016/S0959-4388(00)00203-8
12. Artigas F, Nutt DJ, Shelton R (2002) Mechanism of action of antidepressants. Psychopharmacol Bull 36(Suppl 2):123–132
13. Tanis KQ, Duman RS (2007) Intracellular signaling pathways pave roads to recovery for mood disorders. Ann Med 39:531–544. doi:10.1080/07853890701483270
14. Ohno S, Nishizuka Y (2002) Protein kinase C isotypes and their specific functions: prologue. J Biochem 132:509–511
15. Wetsel WC, Khan WA, Merchenthaler I et al (1992) Tissue and cellular distribution of the extended family of protein kinase C isoenzymes. J Cell Biol 117:121–133
16. Naik MU, Benedikz E, Hernandez I et al (2000) Distribution of protein kinase Mzeta and the complete protein kinase C isoform family in rat brain. J Comp Neurol 426:243–258
17. Tanaka C, Saito N (1992) Localization of subspecies of protein kinase C in the mammalian central nervous system. Neurochem Int 21:499–512
18. Amadio M, Battaini F, Pascale A (2006) The different facets of protein kinases C: old and new players in neuronal signal transduction pathways. Pharmacol Res 54:317–325. doi:10.1016/j.phrs.2006.08.002
19. Boehm J, Kang M-G, Johnson RC et al (2006) Synaptic Incorporation of AMPA Receptors during LTP Is Controlled by a PKC Phosphorylation Site on GluR1. Neuron 51:213–225. doi:10.1016/j.neuron.2006.06.013
20. Dai S, Hall DD, Hell JW (2009) Supramolecular assemblies and localized regulation of voltage-gated ion channels. Physiol Rev 89:411–452. doi:10.1152/physrev.00029.2007
21. Goode N, Hughes K, Woodgett JR, Parker PJ (1992) Differential regulation of glycogen synthase kinase-3 beta by protein kinase C isotypes. J Biol Chem 267:16878–16882

22. Huang K-P (1989) The mechanism of protein kinase C activation. Trends Neurosci 12:425–432. doi:10.1016/0166-2236(89)90091-X
23. Jayanthi LD, Samuvel DJ, Blakely RD, Ramamoorthy S (2005) Evidence for biphasic effects of protein kinase C on serotonin transporter function, endocytosis, and phosphorylation. Mol Pharmacol 67:2077–2087. doi:10.1124/mol.104.009555
24. Kolch W, Heidecker G, Kochs G et al (1993) Protein kinase C alpha activates RAF-1 by direct phosphorylation. Nature 364:249–252. doi:10.1sj.npp./364249a0
25. Martelli AM, Evangelisti C, Nyakern M, Manzoli FA (2006) Nuclear protein kinase C. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids 1761:542–551. doi:10.1016/j.bbalip.2006.02.009
26. Morgan A, Burgoyne RD, Barclay JW et al (2005) Regulation of exocytosis by protein kinase C. Biochem Soc Trans 33:1341–1344. doi:10.1042/BST20051341
27. Pasinelli P, Ramakers GM, Urban IJ et al (1995) Long-term potentiation and synaptic protein phosphorylation. Behav Brain Res 66:53–59
28. Yoshimasa T, Sibley DR, Bouvier M et al (1987) Cross-talk between cellular signalling pathways suggested by phorbol-ester-induced adenylate cyclase phosphorylation. Nature 327:67–70. doi:10.1sj.npp./327067a0
29. Hofmann J (1997) The potential for isoenzyme-selective modulation of protein kinase C. FASEB J 11:649–669
30. Nelson TJ, Alkon DL (2009) Neuroprotective versus tumorigenic protein kinase C activators. Trends Biochem Sci 34:136–145. doi:10.1016/j.tibs.2008.11.006
31. Ron D, Kazanietz MG (1999) New insights into the regulation of protein kinase C and novel phorbol ester receptors. FASEB J 13:1658–1676
32. Bitran JA, Manji HK, Potter WZ, Gusovsky F (1995) Down-regulation of PKC alpha by lithium in vitro. Psychopharmacol Bull 31:449–452
33. Manji HK, Lenox RH (1999) Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. Biol Psychiatry 46:1328–1351
34. Manji HK, Etcheberrigaray R, Chen G, Olds JL (1993) Lithium decreases membrane-associated protein kinase C in hippocampus: selectivity for the alpha isozyme. J Neurochem 61:2303–2310
35. Jensen JB, Mørk A (1997) Altered protein phosphorylation in the rat brain following chronic lithium and carbamazepine treatments. Eur Neuropsychopharmacol 7:173–179
36. Lenox RH, Watson DG, Patel J, Ellis J (1992) Chronic lithium administration alters a prominent PKC substrate in rat hippocampus. Brain Res 570:333–340
37. Szabo ST, Machado-Vieira R, Yuan P et al (2009) Glutamate receptors as targets of protein kinase C in the pathophysiology and treatment of animal models of mania. Neuropharmacology 56:47–55. doi:10.1016/j.neuropharm.2008.08.015
38. Chen G, Manji HK, Hawver DB et al (1994) Chronic sodium valproate selectively decreases protein kinase C alpha and epsilon in vitro. J Neurochem 63:2361–2364
39. Basta-Kaim A, Budziszewska B, Jaworska-Feil L et al (2006) Antipsychotic drugs inhibit the human corticotropin-releasing-hormone gene promoter activity in neuro-2A cells-an involvement of protein kinases. Neuropsychopharmacology 31:853–865. doi:10.1038/sj.npp.1300911
40. Moore GJ, Bebchuk JM, Parrish JK et al (1999) Temporal dissociation between lithium-induced changes in frontal lobe myo-inositol and clinical response in manic-depressive illness. Am J Psychiatry 156:1902–1908
41. Mann CD, Vu TB, Hrdina PD (1995) Protein kinase C in rat brain cortex and hippocampus: effect of repeated administration of fluoxetine and desipramine. Br J Pharmacol 115:595–600
42. Rausch JL, Gillespie CF, Fei Y et al (2002) Antidepressant effects on kinase gene expression patterns in rat brain. Neurosci Lett 334:91–94
43. Kim SH, Kim MK, Yu HS et al (2010) Electroconvulsive seizure increases phosphorylation of PKC substrates, including GAP-43, MARCKS, and neurogranin, in rat brain. Prog Neuropsychopharmacol Biol Psychiatry 34:115–121. doi:10.1016/j.pnpbp.2009.10.009
44. Nestler EJ, Hyman SE (2010) Animal models of neuropsychiatric disorders. Nat Neurosci 13:1161–1169. doi:10.1sj.npp./nn.2647
45. Frey BN, Valvassori SS, Réus GZ et al (2006) Effects of lithium and valproate on amphetamine-induced oxidative stress generation in an animal model of mania. J Psychiatry Neurosci 31:326–332
46. Wesołowska A, Partyka A, Jastrzębska-Więsek M et al (2010) Tail suspension test does not detect antidepressant-like properties of atypical antipsychotics. Behav Pharmacol. doi:10.1097/FBP.0b013e3283423d6b
47. Abrial E, Etievant A, Bétry C et al (2011) Manic-like response to amphetamine or sleep deprivation in rats is decreased by protein kinase C inhibition. 10th Meeting of Société des Neurosciences, Marseille, France, May 24–27, 2011
48. Einat H, Yuan P, Szabo ST et al (2007) Protein kinase C inhibition by tamoxifen antagonizes manic-like behavior in rats: implications for the development of novel therapeutics for bipolar disorder. Neuropsychobiology 55:123–131. doi:10.1159/000106054
49. Sabioni P, Baretta IP, Ninomiya EM et al (2008) The antimanic-like effect of tamoxifen: Behavioural comparison with other PKC-inhibiting and antiestrogenic drugs. Prog Neuropsychopharmacol Biol Psychiatry 32:1927–1931. doi:10.1016/j.pnpbp.2008.09.023
50. Browman KE, Kantor L, Richardson S et al (1998) Injection of the protein kinase C inhibitor Ro31-8220 into the nucleus accumbens attenuates the acute response to amphetamine: tissue and behavioral studies. Brain Res 814:112–119
51. Steketee JD (1993) Injection of the protein kinase inhibitor H7 into the A10 dopamine region blocks the acute responses to cocaine: behavioral and in vivo microdialysis studies. Neuropharmacology 32:1289–1297
52. Kantor L, Gnegy ME (1998) Protein kinase C inhibitors block amphetamine-mediated dopamine release in rat striatal slices. J Pharmacol Exp Ther 284:592–598
53. Loweth JA, Svoboda R, Austin JD et al (2009) The PKC inhibitor Ro31-8220 blocks acute amphetamine-induced dopamine overflow in the nucleus accumbens. Neurosci Lett 455:88–92. doi:10.1016/j.neulet.2009.03.012
54. Chen R, Furman CA, Zhang M et al (2009) Protein kinase Cbeta is a critical regulator of dopamine transporter trafficking and regulates the behavioral response to amphetamine in mice. J Pharmacol Exp Ther 328:912–920. doi:10.1124/jpet.108.147959
55. Gessa GL, Pani L, Fadda P, Fratta W (1995) Sleep deprivation in the rat: an animal model of mania. Eur Neuropsychopharmacol 5 (Suppl):89–93
56. Einat H, Manji HK (2006) Cellular Plasticity Cascades: Genes-To-Behavior Pathways in Animal Models of Bipolar Disorder. Biol Psychiatry 59:1160–1171. doi:10.1016/j.biopsych.2005.11.004
57. Cervo L, Mukherjee S, Bertaglia A, Samanin R (1997) Protein kinases A and C are involved in the mechanisms underlying

consolidation of cocaine place conditioning. Brain Res 775:30–36
58. Lai Y-T, Fan H-Y, Cherng CG et al (2008) Activation of amygdaloid PKC pathway is necessary for conditioned cues-provoked cocaine memory performance. Neurobiol Learn Mem 90:164–170. doi:10.1016/j.nlm.2008.03.006
59. Narita M, Akai H, Nagumo Y et al (2004) Implications of protein kinase C in the nucleus accumbens in the development of sensitization to methamphetamine in rats. Neuroscience 127:941–948. doi:10.1016/j.neuroscience.2004.06.017
60. Narita M, Aoki T, Ozaki S et al (2001) Involvement of protein kinase Cgamma isoform in morphine-induced reinforcing effects. Neuroscience 103:309–314
61. Olive MF, Mehmert KK, Messing RO, Hodge CW (2000) Reduced operant ethanol self-administration and in vivo mesolimbic dopamine responses to ethanol in PKCepsilon-deficient mice. Eur J Neurosci 12:4131–4140
62. Abrial E, Haddjeri N, Lambás-Señas L (2010) Effects of protein kinase c inhibitors tamoxifen and chelerythrine on anxiety and depression-like behaviors. FENS Abstr. vol. 5
63. Raygada M, Cho E, Hilakivi-Clarke L (1998) High maternal intake of polyunsaturated fatty acids during pregnancy in mice alters offsprings' aggressive behavior, immobility in the swim test, locomotor activity and brain protein kinase C activity. J Nutr 128:2505–2511
64. Birnbaum SG, Yuan PX, Wang M et al (2004) Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. Science 306:882–884. doi:10.1126/science.1100021
65. Hains AB, Vu MAT, Maciejewski PK et al (2009) Inhibition of protein kinase C signaling protects prefrontal cortex dendritic spines and cognition from the effects of chronic stress. Proc Natl Acad Sci U S A 106:17957–17962. doi:10.1073/pnas.0908563106
66. Palumbo ML, Zorrilla Zubilete MA, Cremaschi GA, Genaro AM (2009) Different effect of chronic stress on learning and memory in BALB/c and C57BL/6 inbred mice: Involvement of hippocampal NO production and PKC activity. Stress 12:350–361. doi:10.1080/10253890802506383
67. Park S-H, Choi S-H, Lee J et al (2008) Effects of repeated citalopram treatments on chronic mild stress-induced growth associated protein-43 mRNA expression in rat hippocampus. Korean J Physiol Pharmacol 12:117–123. doi:10.4196/kjpp.2008.12.3.117
68. Han F, Shioda N, Moriguchi S et al (2008) Spiro[imidazo[1,2-a]pyridine-3,2-indan]-2(3H)-one (ZSET1446/ST101) treatment rescues olfactory bulbectomy-induced memory impairment by activating Ca2+/calmodulin kinase II and protein kinase C in mouse hippocampus. J Pharmacol Exp Ther 326:127–134. doi:10.1124/jpet.108.137471
69. Moriguchi S, Han F, Nakagawasai O et al (2006) Decreased calcium/calmodulin-dependent protein kinase II and protein kinase C activities mediate impairment of hippocampal long-term potentiation in the olfactory bulbectomized mice. J Neurochem 97:22–29. doi:10.1111/j.1471-4159.2006.03710.x
70. Dwivedi Y, Mondal AC, Rizavi HS et al (2005) Single and repeated stress-induced modulation of phospholipase C catalytic activity and expression: role in LH behavior. Neuropsychopharmacology 30:473–483. doi:10.1038/sj.npp.1300605
71. Wu J, Song T-B, Li Y-J et al (2007) Prenatal restraint stress impairs learning and memory and hippocampal PKCbeta1 expression and translocation in offspring rats. Brain Res 1141:205–213. doi:10.1016/j.brainres.2007.01.024
72. Alfonso J, Frick LR, Silberman DM et al (2006) Regulation of Hippocampal Gene Expression Is Conserved in Two Species Subjected to Different Stressors and Antidepressant Treatments. Biol Psychiatry 59:244–251. doi:10.1016/j.biopsych.2005.06.036
73. Zheng H, Ma G-yu, Fu X-chun, DU H-guang (2008) Effects of paroxetine on protein kinase PKA, PKC and CaMKII activity in different brain regions in a rat depression model. Nan Fang Yi Ke Da Xue Xue Bao 28:1223–1225
74. Lueptow LM, Zhao Z, O'Donnell JM (2010) Norepinephrine and serotonin transporter regulation is important for antidepressant-like effects on behavior in rats. SFN abstr. 2010
75. Sun M-K, Alkon DL (2005) Dual effects of bryostatin-1 on spatial memory and depression. Eur J Pharmacol 512:43–51. doi:10.1016/j.ejphar.2005.02.028
76. Baum AE, Akula N, Cabanero M et al (2008) A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. Mol Psychiatry 13:197–207. doi:10.1038/sj.mp.4002012
77. Burton PR, Clayton DG, Cardon LR (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447:661–678. doi: 10.1sj.npp./nature05911
78. Turecki G, Grof P, Cavazzoni P et al (1998) Evidence for a role of phospholipase C-gamma1 in the pathogenesis of bipolar disorder. Mol Psychiatry 3:534–538
79. Ohnishi T, Yamada K, Ohba H et al (2007) A promoter haplotype of the inositol monophosphatase 2 gene (IMPA2) at 18p11.2 confers a possible risk for bipolar disorder by enhancing transcription. Neuropsychopharmacology 32:1727–1737. doi:10.1038/sj.npp.1301307
80. Sjøholt G, Ebstein RP, Lie RT et al (2004) Examination of IMPA1 and IMPA2 genes in manic-depressive patients: association between IMPA2 promoter polymorphisms and bipolar disorder. Mol Psychiatry 9:621–629. doi:10.1038/sj.mp.4001460
81. Pandey GN, Dwivedi Y, Pandey SC et al (1997) Protein kinase C in the postmortem brain of teenage suicide victims. Neurosci Lett 228:111–114
82. Pandey GN, Dwivedi Y, Rizavi HS et al (2004) Decreased catalytic activity and expression of protein kinase C isozymes in teenage suicide victims: a postmortem brain study. Arch Gen Psychiatry 61:685–693. doi:10.1001/archpsyc.61.7.685
83. Wang HY, Friedman E (1996) Enhanced protein kinase C activity and translocation in bipolar affective disorder brains. Biol Psychiatry 40:568–575
84. Jope RS, Song L, Li PP et al (1996) The phosphoinositide signal transduction system is impaired in bipolar affective disorder brain. J Neurochem 66:2402–2409
85. Mathews R, Li PP, Young LT et al (1997) Increased G alpha q/11 immunoreactivity in postmortem occipital cortex from patients with bipolar affective disorder. Biol Psychiatry 41:649–656. doi:10.1016/S0006-3223(96)00113-8
86. Shelton RC, Hal Manier D, Lewis DA (2009) Protein kinases A and C in post-mortem prefrontal cortex from persons with major depression and normal controls. Int J Neuropsychopharmacol 12:1223–1232. doi:10.1017/S1461145709000285
87. Pandey GN, Dwivedi Y, Ren X et al (2003) Altered expression and phosphorylation of myristoylated alanine-rich C kinase substrate (MARCKS) in postmortem brain of suicide victims with or without depression. J Psychiatr Res 37:421–432
88. Ohmori S, Sakai N, Shirai Y et al (2000) Importance of protein kinase C targeting for the phosphorylation of its substrate, myristoylated alanine-rich C-kinase substrate. J Biol Chem 275:26449–26457. doi:10.1074/jbc.M003588200
89. Wang HY, Markowitz P, Levinson D et al (1999) Increased membrane-associated protein kinase C activity and translocation in blood platelets from bipolar affective disorder patients. J Psychiatr Res 33:171–179

90. Friedman E, Wang HY, Levinson D et al (1993) Altered platelet protein kinase C activity in bipolar affective disorder, manic episode. Biol Psychiatry 33:520–525
91. Hahn C-G, Umapathy C, Wang H-Y et al (2005) Lithium and valproic acid treatments reduce PKC activation and receptor-G protein coupling in platelets of bipolar manic patients. J Psychiatr Res 39:355–363
92. Pandey GN, Ren X, Dwivedi Y, Pavuluri MN (2008) Decreased protein kinase C (PKC) in platelets of pediatric bipolar patients: effect of treatment with mood stabilizing drugs. J Psychiatr Res 42:106–116. doi:10.1016/j.jpsychires.2006.11.004
93. Young LT, Wang JF, Woods CM, Robb JC (1999) Platelet protein kinase C alpha levels in drug-free and lithium-treated subjects with bipolar disorder. Neuropsychobiology 40:63–66
94. Pandey GN, Dwivedi Y, SridharaRao J et al (2002) Protein kinase C and phospholipase C activity and expression of their specific isozymes is decreased and expression of MARCKS is increased in platelets of bipolar but not in unipolar patients. Neuropsychopharmacology 26:216–228. doi:10.1016/S0893-133X(01)00327-X
95. Bebchuk JM, Arfken CL, Dolan-Manji S et al (2000) A preliminary investigation of a protein kinase C inhibitor in the treatment of acute mania. Arch Gen Psychiatry 57:95–97
96. Amrollahi Z, Rezaei F, Salehi B et al (2010) Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. J Affect Disord 129:327–331. doi:10.1016/j.jad.2010.08.015
97. Kulkarni J, Garland KA, Scaffidi A et al (2006) A pilot study of hormone modulation as a new treatment for mania in women with bipolar affective disorder. Psychoneuroendocrinology 31:543–547. doi:10.1016/j.psyneuen.2005.11.001
98. Yildiz A, Guleryuz S, Ankerst DP et al (2008) Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. Arch Gen Psychiatry 65:255–263. doi:10.1001/archgenpsychiatry.2007.43
99. Zarate CA, Singh JB, Carlson PJ et al (2007) Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. Bipolar Disord 9:561–570. doi:10.1111/j.1399-5618.2007.00530.x
100. Yildiz A, Vieta E, Leucht S, Baldessarini RJ (2011) Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. Neuropsychopharmacology 36:375–389. doi:10.1038/npp.2010.192
101. Saraiva L, Fresco P, Pinto E, Gonçalves J (2003) Isoform-selectivity of PKC inhibitors acting at the regulatory and catalytic domain of mammalian PKC-alpha, -betaI, -delta, -eta and -zeta. J Enzyme Inhib Med Chem 18:475–483. doi:10.1080/14756360310001603158
102. Mallinger AG, Thase ME, Haskett R et al (2008) Verapamil augmentation of lithium treatment improves outcome in mania unresponsive to lithium alone: preliminary findings and a discussion of therapeutic mechanisms. Bipolar Disord 10:856–866. doi:10.1111/j.1399-5618.2008.00636.x
103. Schou M (1976) Pharmacology and toxicology of lithium. Annu Rev Pharmacol Toxicol 16:231–243. doi:10.1146/annurev.pa.16.040176.001311
104. Tang P, Roldan G, Brasher PMA et al (2006) A phase II study of carboplatin and chronic high-dose tamoxifen in patients with recurrent malignant glioma. J Neurooncol 78:311–316. doi:10.1007/s11060-005-9104-y
105. Thompson DS, Spanier CA, Vogel VG (1999) The Relationship Between Tamoxifen, Estrogen, and Depressive Symptoms. Breast J 5:375–382
106. Nelson TJ, Cui C, Luo Y, Alkon DL (2009) Reduction of beta-amyloid levels by novel protein kinase C(epsilon) activators. J Biol Chem 284:34514–34521. doi:10.1074/jbc.M109.016683
107. Pacheco MA, Stockmeier C, Meltzer HY et al (1996) Alterations in phosphoinositide signaling and G-protein levels in depressed suicide brain. Brain Res 723:37–45
108. Coull MA, Lowther S, Katona CL, Horton RW (2000) Altered brain protein kinase C in depression: a post-mortem study. Eur Neuropsychopharmacol 10:283–288
109. Hrdina P, Faludi G, Li Q et al (1998) Growth-associated protein (GAP-43), its mRNA, and protein kinase C (PKC) isoenzymes in brain regions of depressed suicides. Mol Psychiatry 3:411–418
110. Soares JC, Chen G, Dippold CS et al (2000) Concurrent measures of protein kinase C and phosphoinositides in lithium-treated bipolar patients and healthy individuals: a preliminary study. Psychiatry Res 95:109–118
111. Pandey GN, Dwivedi Y, Kumari R, Janicak PG (1998) Protein kinase C in platelets of depressed patients. Biol Psychiatry 44:909–911