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Ameliorating prefrontal cortical dysfunction in mental illness: inhibition of phosphatidylinositol-protein kinase C signaling

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Abstract

Background—Bipolar disorder and schizophrenia are associated with profound dysfunction of the prefrontal cortex (PFC), with bipolar disorder most associated with changes in ventromedial PFC and schizophrenia more associated with changes in dorsolateral PFC.

Discussion—Recent genetic and biochemical studies have also linked these illnesses to disinhibition of phosphatidylinositol-protein kinase C signaling. For example, DAG kinase eta, an enzyme that metabolizes DAG and thus reduces protein kinase C activity, is the gene most altered in bipolar disorder. Similarly, regulator of G protein signaling 4 is the molecule most altered in the PFC of patients with schizophrenia, and this molecule normally serves to inhibit Gq signaling. Animal studies have shown that high levels of phosphatidylinositol-protein kinase C signaling in the PFC markedly impair PFC function at the behavioral and cellular levels. Most importantly, many effective medications for bipolar disorder and schizophrenia inhibit phosphatidylinositol-protein kinase C signaling, either through intracellular actions (lithium, valproate) or through extra-cellular blockade of receptors coupled to this pathway (5HT₂ receptors and alpha-1 adrenoceptors). Recent data suggest that lithium and valproate can protect gray matter in patients with bipolar disorder. These findings encourage the development of protein kinase C inhibitors for the treatment of mental illness.

Keywords

Schizophrenia; Bipolar disorder; Mania; PTSD; Working memory; Chelerythrine; Lithium; Valproate; Atypical; Antipsychotic; Frontal lobe

Our knowledge of the neural bases of mental illness has made tremendous progress over the last two decades: there has been a confluence in our understanding of the molecular regulation of higher order neural circuits and their relationship to genetic and neuropathological alterations in mental illness (Arnsten and Manji 2008). In particular, we have gained greater understanding of the prefrontal cortex (PFC)—the brain region most afflicted in psychiatric disorders. We have come to understand the key role of PFC circuits in the regulation of thought, emotion, and action and have begun to reveal the powerful modulatory influences on PFC networks. These basic studies have provided a rational basis for understanding how genetic insults may lead to PFC dysfunction and the symptoms of mental illness and how thoughtfully chosen pharmacological treatments may normalize PFC function. Much of this research has focused attention on the phosphatidylinositol-protein kinase C intracellular signaling pathway, as overactivity of this pathway impairs PFC function (Birnbaum et al. 2004), while agents that

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reduce the activity of this pathway are common treatments for serious mental illness (Manji et al. 1999).

Functions of PFC

The PFC intelligently guides thought, emotion, and actions, orchestrating the brain's responses through its extensive cortical and subcortical projections (Goldman-Rakic 1987). Networks of PFC neurons are able to represent goals in the absence of environmental stimulation, providing great powers of abstraction and inhibition (Goldman-Rakic 1995). These PFC abilities are those most weakened in mental illness (Blumberg et al. 1999; Goldman-Rakic 1991; Weinberger et al. 1986).

The PFC in primates is functionally specialized, with the dorsolateral regions regulating cognition and action (Jacobsen 1936; Fuster 1984; Goldman and Rosvold 1970; Goldman-Rakic et al. 1992; Petrides 1986) and the ventromedial regions (including the orbital prefrontal cortices) regulating emotion (Dias et al. 1996; Iversen and Mishkin 1970). Anterior medial aspects of PFC are also important for monitoring errors (Lütcke and Frahm 2008), and most anteriorly, for understanding what is real (so-called reality monitoring; Simons et al. 2008). Thus, lesions to the dorsal and/or lateral PFC produce deficits in working memory (our mental sketchpad), in attention regulation (set-shifting, dividing attention, sustaining attention, and inhibiting distractions), and in the planning and sculpting of actions (Gazzaley et al. 2007; Goldman-Rakic 1996; Robbins 1996; 2007). Dorsolateral PFC is critical for abstraction (e.g., categorization) and the cognitive aspects of higher order decision-making, contributing to insight (Bunge et al. 2003; Wallis et al. 2001). These regions of PFC are also important for the encoding and retrieval of memories (memory recall) and for the suppression of inappropriate memories (proactive interference; Bunge et al. 2001; Lepage et al. 2000). Thus, large bilateral lesions of the dorsolateral PFC produce profound impairment in cognitive state. In contrast, lesions to ventral PFC produce a disinhibited emotional state, e.g., weakening regulation of aggressive and sexual impulses (Stuss et al. 1992) and altering response to reward vs. punishment (Floden et al. 2008). Damage to the ventromedial PFC early in development is even associated with sociopathy (Anderson et al. 1999).

In humans, there is also specialization by hemisphere, with the left hemisphere specialized for the *generation* of language, and possibly other cognitive and affective spheres, and the right hemisphere specialized for *inhibition* of behavior, thought, and emotion. Thus, lesions to the left PFC are often associated with depression (Morris et al. 1996), while lesions to the right PFC are associated with a disinhibited profile. For example, lesions to the right PFC are associated with risky behaviors on a gambling task (Clark et al. 2003), an impaired ability to sustain attention (Wilkins et al. 1987) and with increased distractibility (Woods and Knight 1986). The right, inferior PFC has been shown to be critical for impulse control (Aron et al. 2004; Rubia et al. 2003), and transcranial magnetic stimulation to this region—using a sequence that weakens function—induces poor impulse control and an inability to stop motor responses in normal control subjects (Chambers et al. 2006). The right PFC is also activated during associative learning (Corlett et al. 2004), while reduced activity in this area is associated with delusions in patients (Corlett et al. 2007) and in normal volunteers given ketamine (Corlett et al. 2006).

The PFC is able to guide thought, behavior, and emotion by representing goals and stimuli not present in the environment. This representational knowledge is created by networks of PFC neurons engaged in recurrent excitation, tuned by GABA interneurons (Goldman-Rakic 1987, 1995). Recent studies have shown that the persistent activity and tuning of PFC networks are also profoundly altered by the catecholamines, norepinephrine (NE), and dopamine (DA; Arnsten 2007). This is an exquisite and highly sensitive process whereby either too little or too

much NE or DA greatly impairs PFC function (Arnsten 2007; Arnsten and Goldman-Rakic 1990; Ramos and Arnsten 2007; Vijayraghavan et al. 2007).

The PFC is powerfully modulated by catecholamine activation of intracellular signaling cascades

It has been appreciated for almost 30 years that catecholamines are essential to the working memory functions of the dorsolateral PFC (Brozoski et al. 1979). Levels of catecholamines change in PFC according to arousal state and are likely responsible for many changes in the strength of PFC abilities with changing environmental demands.

Catecholamines are released in PFC according to state of arousal

Under nonstress, alert conditions, NE and DA cells in the brainstem increase their firing to stimuli and events in the environment according to their behavioral meaning and/or reward relevance (Aston-Jones et al. 2000; Foote et al. 1983; Schultz 1998). Thus, optimal levels of catecholamines would likely be available to modulate PFC networks in the alert, nonstressed state. In contrast, inadequate catecholamines are likely available when the subject is tired or drowsy, as NE cells fire at very slow rates when the animal is drowsy, and are silent during REM sleep (Foote et al. 1983). In contrast, locus coeruleus (LC) neurons have very high baseline firing when the animal is anxious or agitated (Aston-Jones et al. 1994). These firing patterns are consistent with biochemical studies of PFC, whereby exposure to even quite mild uncontrollable stress leads to high levels of NE and DA release in PFC (Deutch et al. 1990; Finlay et al. 1995). In concert with these findings, NE's beneficial actions occur at alpha-2A receptors with high affinity for NE (Arnsten 2000; Arnsten and Goldman-Rakic 1985; Li and Mei 1994), while lower affinity alpha-1 (Arnsten et al. 1999; Mao et al. 1999) and beta receptors (Ramos et al. 2005) contribute to detrimental effects on PFC function, e.g., as observed during stress (Birnbaum et al. 1999).

PFC regional sensitivity to monoamine actions

The working memory functions of the dorsolateral PFC are highly sensitive to changes in catecholamines, as will be described in detail below (Brozoski et al. 1979; Roberts et al. 1994). Catecholamines in lateral PFC are also important for the attentional set-shifting properties of this region, with DA needed to establish attentional set (Crofts et al. 2001), and NE likely needed to shift set (Tait et al. 2007). NE is also important for the operations of the more ventrolateral PFC including behavioral inhibition (Chamberlain et al. 2007) and conditional motor responding (Wang et al. 2004). In contrast, studies of the reversal operations of the orbital PFC indicate that serotonin is especially important to this region (Clarke et al. 2007), although more detailed analyses indicate that catecholamines influence some orbital functions as well (e.g., Steere and Arnsten 1997).

The detailed receptor and intracellular mechanisms influencing PFC network physiology have been limited to dorsolateral PFC networks in monkeys performing a spatial working memory task. It is likely that some of these findings will apply to other PFC regions and cognitive operations as well, especially if they require representations of information such as goals, complex network interactions and/or inhibition of prepotent responses. However, some findings may not generalize, and thus caution is warranted. Studies of rat behavior referenced below utilized the spatial delayed alternation task performed in a T maze, a test that requires spatial working memory, behavioral inhibition (inhibiting the tendency to return to a rewarded location), and regulation of distractibility (the rats are picked up and returned to the start box on each trial). Thus, these findings likely apply across this range of PFC operations.

Optimal levels of catecholamines are needed for tuned, persistent firing

Optimal spatial working memory requires the persistent firing of a network of PFC pyramidal neurons during the delay period when the correct spatial location must be kept “in mind” (Goldman-Rakic 1995). This network must also display spatial specificity, and not fire during the delay period following other spatial locations. Optimal levels of NE and DA make distinct contributions to these physiological requirements: moderate levels of NE strengthen persistent firing for the preferred spatial direction through actions at post-synaptic alpha-2A receptors that have high affinity for NE (Li et al. 1999; Wang et al. 2007). Conversely, moderate levels of DA suppress the neuron’s responses to nonpreferred spatial directions through actions at D1 receptors (Vijayraghavan et al. 2007). Thus, alpha-2A enhances “signals”, while D1 reduces “noise” (Arnsten 2007). These actions are accomplished through opposite effects on cAMP–hyperpolarization-activated cyclic nucleotide-gated ion channels (HCN) signaling, with alpha-2A receptors inhibiting cAMP–HCN signaling leading to strengthening of shared network inputs on spines (Wang et al. 2007), and D1 receptors stimulating cAMP–HCN signaling, weakening nonshared inputs on different spines (details describing these beneficial actions can be found in Arnsten 2007). Based on this research in animals, the alpha-2A agonist, guanfacine, is now in widespread use in the USA to treat PFC disorders in humans (e.g., Biederman et al. 2008; Scahill et al. 2001). The therapeutic effects of guanfacine have been shown to be independent of its sedating effects (Arnsten et al. 1988; Arnsten et al. 1996; Biederman et al. 2008) and likely arise from actions directly in PFC (Avery et al. 2000; Mao et al. 1999; Ramos et al. 2006; Swartz et al. 2000; Wang et al. 2007). D1 agonists are not yet available for human trials, but may not be an ideal medication, as optimal D1 receptor stimulation likely requires dynamic alterations based on cognitive demands rather than the steady state provided by drug therapy (Vijayraghavan et al. 2007).

High levels of catecholamine release during stress reduce network firing and impair PFC function

High levels of NE and DA release in the PFC during stress erode PFC network physiology and function (Arnsten 1998). High levels of NE release during stress engage adrenoceptors with lower affinity for NE, i.e., the alpha-1 and beta receptors (Arnsten 2000). Stimulation of alpha-1 or beta-1 receptors impairs PFC functions (Arnsten et al. 1999; Ramos et al. 2005), as does very high levels of DA D1 receptor stimulation (Murphy et al. 1996; Zahrt et al. 1997). These detrimental actions occur via excessive cAMP–HCN channel signaling (Vijayraghavan et al. 2007; Wang et al. 2007), and through activation of phosphatidylinositol-protein kinase C signaling (Birnbaum et al. 2004).

cAMP–HCN signaling

High levels of cAMP generation during stress exposure open a large number of HCN channels, weakening both preferred and nonpreferred inputs to the cell, thus inducing network collapse (Wang et al. 2007). A variety of treatments increases cAMP silence network firing, and network activity is restored if HCN channels are then blocked (ibid). High levels of cAMP may also promote phosphatidylinositol signaling, e.g., through phosphorylation of IP3 receptors (Soulsby and Wojcikiewicz 2005). Thus, these intracellular pathways act in concert to induce rapid and marked loss of PFC function.

Phosphatidylinositol-protein kinase C signaling

Protein kinase C is activated by a series of chemical events (Berridge 1989). Neurotransmitter receptors on cell membranes (e.g., the noradrenergic alpha-1 receptor, the serotonergic 5HT_{2A} receptor, or the metabotropic glutamate receptors), couple to Gq proteins, which in turn activate phospholipase C. Phospholipase C in turn cleaves PIP₂ to form IP₃ and DAG. IP₃ interacts with receptors on the endoplasmic reticulum to release calcium from intracellular

stores. The released calcium then facilitates the translocation of protein kinase C to the cell membrane, where it is activated by DAG. Importantly, an enzyme called DAG kinase inhibits the activity of this pathway, phosphorylating DAG as an initial step in recycling DAG back to PIP2. Thus, DAG kinase reduces protein kinase C activity. Another important molecular brake on this pathway is regulator of G protein signaling 4 (RGS4), which inhibits Gq and arrests signaling through this pathway. As will be described below, both RGS4 and DAG kinase are altered in mental illness.

Basal levels of intracellular calcium release are vital for neuronal housekeeping functions such as transmitter release from axonal terminals (Berridge 1989). These pathways also are likely involved with controlling neuronal excitability in PFC (e.g., Aghajanian and Marek 1997). However, high levels of protein kinase C intracellular signaling rapidly and markedly impair prefrontal cortical function (Birnbaum et al. 2004).

PKC activity is increased in the PFC following exposure to even quite mild, uncontrollable stress (Birnbaum et al. 2004). Stress exposure increases norepinephrine release in the PFC (Finlay et al. 1995), which stimulates alpha-1 receptors and activates the phosphatidylinositol signaling pathway (Birnbaum et al. 2004). These actions greatly impair prefrontal function. Thus, prefrontal cortical cognitive deficits are observed following exposure to stress, stimulation of alpha-1 receptors, or direct activation of PKC with phorbol esters in the PFC (Birnbaum et al. 2004; Runyan et al. 2005). Conversely, inhibition of PKC restores prefrontal cognitive function following all of these conditions (Birnbaum et al. 2004; Runyan et al. 2005). The detrimental effects of PKC activation are also observed at the level of single cells, where the firing of prefrontal cortical neurons during cognitive tasks is markedly reduced by activation of PKC and restored by inhibition of PKC (Birnbaum et al. 2004). PKC inhibition also improves working memory performance in aged rats and monkeys, who may have increased PKC signaling with advancing age (Brennan et al. 2008a). Activation of the IP3 arm of this signaling pathway also suppresses PFC neuronal firing. Calcium imaging and intracellular recordings from layer V neurons in a PFC slice preparation show a suppression of cell firing as the calcium wave invades the soma and opens SK channels (Hagenston et al. 2008). Conversely, blockade of IP3 receptors in the rat PFC improves delayed alternation performance (Brennan et al. 2008b). Thus, the ability of the PFC to regulate emotion, thought, and action is markedly impaired by overactivity of phosphatidylinositol-protein kinase C signaling.

Structural losses with chronic stress

In rats, chronic exposure to stress leads to retraction of prefrontal cortical dendrites and loss of dendritic spines (Liston et al. 2006; Radley et al. 2005; Radley et al. 2006). This loss of gray matter appears to involve elevated protein kinase C signaling (Hains et al. 2008). Protein kinase C also interacts with other intracellular pathways such as glycogen synthase 3 and ERK MAP kinase pathways that regulate cell survival (Shaltiel et al. 2007). These findings are highly relevant to mental illness, as there is loss of PFC gray matter in both schizophrenia and bipolar disorder (see below).

PFC dysfunction in post-traumatic stress disorder (PTSD), bipolar disorder, and schizophrenia

Disturbances of PFC function are the most common finding in mental disorders. Many common symptoms of mental illness, e.g., distractibility, poor concentration, loss of insight, poor error monitoring and reality testing, weak emotional regulation, forgetfulness, disorganization, are signs of PFC dysfunction. Functional imaging studies of patients with mental illness commonly demonstrate hypo-frontality, while structural imaging and post-mortem neuropathological

studies often observe loss of PFC gray matter and/or reduction in spine density. These findings are consistent with the profound changes in PFC functions in these patient populations. The use of modern imaging methods has even allowed these approaches to be applied to symptoms such as delusions and hallucinations that were formerly thought to be beyond the bounds of scientific inquiry. A very brief review of this field follows.

Post-traumatic stress disorder

PTSD is an anxiety disorder precipitated by an extreme stressor or traumatic event such as war, a natural disaster, or physical/sexual abuse. PTSD is characterized by intrusive re-experiencing of a trauma that can be so vivid that the patient feels that it is actually happening (a so-called flashback). Symptoms include also include hypervigilance and impaired executive operations of the PFC (Bremner 2002; Golier and Yehuda 2002; Shin et al. 2006; Yehuda et al. 1995). PTSD is commonly associated with overactivity of the NE system arising from the locus coeruleus, hyperactivation of the amygdala, and hypoactivation of the PFC (for review, see Bremner et al. 2008). Medial PFC volume is reduced and underactive during symptomatic states, and these medial PFC deficits are inversely proportional to PTSD symptom severity (for review, see Shin et al. 2006). Underactivity of the PFC likely contributes to a patient's inability to suppress traumatic memories and to modulate amygdala and noradrenergic LC activation, resulting in anxiety and hypervigilance. Since dysfunction of the medial PFC is related to impaired error and reality monitoring (Simons et al. 2008; van Veen and Carter 2002), these findings may also serve to explain why patients confuse vivid memories with reality during flashbacks.

Bipolar disorder

Patients with bipolar disorder cycle between periods of mania and depression. The symptoms of mania include increased risk taking, distractibility, and reduced inhibition, and when severe, psychotic delusions and hallucinations. Neuropsychological studies indicate patients are also impaired in attention and reversal tasks during the depressed phase (Murphy et al. 2001). Some evidence of impaired cognitive control and executive function also persists during periods of remission (euthymia) in patients, suggesting that these impairments are inherent to the disease state (Phillips and Vieta 2007).

Given the cycling nature of bipolar disorder, researchers have had the unique opportunity to image patients in the manic vs. euthymic state, and thus compare the patterns of activity related to illness within the same brain. These functional imaging studies have demonstrated marked underactivity of the right PFC in mania, including the right orbital and right polar prefrontal regions, and the right inferior frontal gyrus that is needed for behavioral inhibition (Altshuler et al. 2005; Blumberg et al. 2003; Blumberg et al. 1999; Rubinsztein et al. 2001). Indeed, transcranial magnetic stimulation to the right PFC can actually induce delusions and manic episodes in depressed patients (Ella et al. 2002; Zwanzger et al. 2002). Thus, severe dysfunction of the PFC, particularly in the right hemisphere, is highly consistent with the symptoms of mania. In contrast, the left hemisphere is altered during the depressive phase, consistent with imaging studies of patients with major depressive disorder (Blumberg et al. 2003). Structural imaging studies have also documented reduced volume of the orbital/inferior PFC in patients with bipolar disorder (Blumberg et al. 2006), as well as alterations in medial PFC, temporal lobe, and enlargement of the third ventricle (reviewed in Schloesser et al. 2008). Recent post-mortem neuropathological studies are complementary, showing reductions in cortex volume and region- and layer-specific reductions in number, density, and/or size of neurons and glial cells in the subgenual PFC, orbital cortex, and dorsal anterolateral PFC in an individual with bipolar disorder (Schloesser et al. 2008). Some of these structural changes may involve abnormalities of mitochondrial function (Quiroz et al. 2008), but it is likely that elevated PKC signaling also contributes to loss of gray matter (see above). These imaging findings are consistent with the

established roles of the ventromedial cortex in the regulation of emotion and with the right hemisphere being especially important for the inhibition of inappropriate emotions, thoughts, and behaviors.

Schizophrenia

Impaired cognitive functioning is a fundamental feature of schizophrenia (Barch 2005; Simon et al. 2007), and greatly impoverished executive abilities contribute to the poor functional outcome of patients (Green 2006). Numerous studies indicate that dysfunction of dorsolateral PFC contributes to schizophrenia pathophysiology (e.g., Goldman-Rakic 1991; Lewis et al. 2005; Lewis and Levitt 2002; Weinberger and Berman 1996; Weinberger et al. 1986). While the dorsolateral PFC is the subregion most widely implicated with schizophrenia, recent studies indicate a role for other subregions of the PFC as well. For example, underactivity of the medial anterior and right lateral PFC has been related to impaired reality testing (Simons et al. 2008) and with delusions (Corlett et al. 2007). Furthermore, auditory hallucinations may arise from inadequate corollary discharge from PFC to Wernicke's area during inner speech (Ford et al. 2002), i.e., inadequate tagging that a voice is internally generated. Taken together, these new data represent increasing links between PFC dysfunction, cognitive impairment, and the so-called positive symptoms of psychotic illness.

Structural imaging and post-mortem studies indicate significant alterations in fundamental PFC networks in patients with schizophrenia. For example, neuropathological studies have indicated reductions in neuropil in the dorsolateral PFC of patients with schizophrenia (Selemon and Goldman-Rakic 1999), including reduced inhibitory connections (Lewis et al. 2005) and reduced dendritic spines, the sites of excitatory network connections (Glantz and Lewis 2000). Thus, there is a loss of substrate for PFC network connections in schizophrenia.

Genetic alterations in schizophrenia and bipolar disorder include molecules that brake stress pathways

Great advances are being made in the genetics of severe mental illness. Many of the genes associated with these disorders play important roles in cortical development and glutamate receptor transmission (Owen et al. 2005). However, many of these genes also encode for molecules that serve as molecular brakes on the intracellular stress pathways. For example, disrupted in schizophrenia (DISC1) regulates cAMP concentrations by activating phosphodiesterases. Two other important gene products, RGS4 and DAG kinase, inhibit phosphatidylinositol-protein kinase C signaling. Their roles in the pathway are illustrated in Fig. 1.

RGS4 inhibits Gq signaling by activating a GTPase that drives Gq into an inactive, GDP-bound form (Hepler et al. 1997). Microarray studies have shown that RGS4 is the molecule most altered in the PFC of patients with schizophrenia (Mirnics et al. 2001). Measures of RGS4 mRNA and protein have replicated this finding of marked reductions in PFC of patients with schizophrenia (Erdely et al. 2006). Genetic studies have also shown some associations between schizophrenia and polymorphisms of the RGS4 gene (Chowdari et al. 2002; Levitt et al. 2006; Talkowski et al. 2006). Loss of RGS4 in PFC would lead to disinhibited protein kinase C signaling and impaired PFC function.

DAG kinase (DGKH) is a member of the family of diacylglycerol kinases (DGKs) that play a major role in regulating the phosphoinositide signaling pathway. As noted above, hydrolysis of PIP₂ produces the intracellular second messenger DAG, which serves as an allosteric activator of protein kinase C (Newton 1997). This pathway is tightly regulated, and the major route of DAG metabolism is its conversion to phosphatidic acid by the DGKs (Topham

2006; Topham and Prescott 1999). Thus, even modest impairments in the function of DGKs can result in a dysregulation of PKC signaling.

Recently, two completely independent genome-wide association studies have identified DGKH as a risk gene for bipolar disorder. In the NIMH study, over 550,000 single nucleotide polymorphisms (SNPs) were genotyped in two independent case-control samples (Baum et al. 2008). The 37 most significant SNPs were individually genotyped, and of these, the strongest association signal ($p=1.5\times 10^{-8}$) was at a polymorphism in the DGKH gene. A second genome-wide association study by the Wellcome Trust Case Control Consortium (Wellcome 2007) investigated a different array of SNPs and found several in DGKH that were associated with bipolar disorder at the 10^{-3} level. Thus, bipolar disorder is associated with dysregulation of protein kinase C signaling.

Genetic weakness in the molecular “brakes” on protein kinase C signaling would lead to exaggerated increases in protein kinase C signaling in the PFC during stress exposure and more profound deficits in PFC function. These findings are consistent with the common observation that stress exposure is often the trigger for manic episodes (Hammen and Gitlin 1997) and for psychotic relapse in schizophrenia (Breier et al. 1991).

Treatments for mental disorders inhibit PKC signaling

The interactions between medications and the phosphatidylinositol-protein kinase C signaling pathway are illustrated in Fig. 1.

The importance of protein kinase C signaling to the pathophysiology and treatment of mania was first recognized by Husseini Manji (Manji et al. 1999; Manji and Lenox 1999). Manji’s lab discovered that two very dissimilar treatments for mania—the simple ion lithium and the fatty acid valproate—both shared the property of reducing protein kinase C following chronic treatment (Zarate et al. 2006). These findings indicated that direct protein kinase C inhibitors should be effective in treating mania. Proof of concept trials have been conducted with the one compound approved for human use that inhibits protein kinase C and yet crosses the blood-brain barrier—tamoxifen (Bebchuk et al. 2000). Tamoxifen is an anti-estrogen with protein kinase C inhibitory properties at high doses (its anti-estrogen effects preclude its use as a therapeutic for this indication). Tamoxifen has been found to be very successful in reducing manic symptoms in double-blind trials (Yildiz et al. 2008; Zarate et al. 2007). Antimanic effects were found as early as day 5 in the Zarate study, when the increasing dose of tamoxifen became sufficient to inhibit CNS protein kinase C activity. In view of the several week delay in the treatment of mania observed with lithium, these results suggest that directly inhibiting protein kinase C may allow a more rapid treatment of mania. Thus, new treatments are needed that inhibit protein kinase C and get into brain. It is also important to note that the agents described above inhibit protein kinase C with low, micromolar affinity (O’Brian et al. 1985), thus leaving critical housekeeping functions of this kinase intact (e.g., transmitter release).

Inhibition of protein kinase C signaling is also highly relevant to the treatment of schizophrenia. Most atypical antipsychotics block 5HT₂ (Schotte et al. 1996) and α -1 adrenoceptors (Bymaster et al. 1996; Schotte et al. 1993), both of which are coupled to Gq phosphatidylinositol signaling. These findings may be of particular relevance to PFC dysfunction in schizophrenia, given the extensive loss of RGS4 in the PFC of patients with schizophrenia (Erdely et al. 2006; Mirnics et al. 2001).

Treatments that block α -1 receptors are also in use for the treatment of PTSD. Atypical antipsychotics are in common use for this indication (Pae et al. 2008), and the α -1 adrenoceptor antagonist, prazosin, is currently in use for the treatment of PTSD (Raskind et al. 2003; Taylor and Raskind 2002). Chronic stress amplifies NE transmission in PFC (Miner

et al. 2006), and PTSD is a hyper-noradrenergic disorder (Southwick et al. 1999). Thus, blockade of NE's detrimental actions at alpha-1 adreno-ceptors may be especially useful in patients with a history of traumatic stress.

Intriguingly, medications that inhibit protein kinase C appear to normalize PFC gray matter in patients with bipolar disorder. Lithium has been found to increase gray matter volumes in a longitudinal study in bipolar patients (Moore et al. 2000). Additionally, several independent cross-sectional studies have now demonstrated that lithium-treated bipolar patients show increased gray matter volumes compared to untreated bipolar patients (Bearden et al. 2007; Chang et al. 2005; Sassi et al. 2004; Sassi et al. 2002). Importantly, Blumberg et al. (2006) observed a rapid decline in ventral PFC volumes with age in adolescents and young adults with bipolar disorder that were ameliorated by treatment with lithium or valproate. These trophic effects may involve several mechanisms (including GSK-3 inhibition and bcl-2 upregulation), but likely involve protein kinase C inhibition as well. The atypical antipsychotics clozapine and olanzapine may retard loss of PFC volume in patients with schizophrenia (van Haren et al. 2007), and loss of PFC volume appears to be key to the onset of illness (Sun et al. 2008). Thus, protecting PFC circuits likely plays an important role in preventing severe mental illness.

Future research

Future studies in animals and humans are needed to directly test the hypothesis that inhibition of PKC signaling will be helpful in protecting PFC functions in patients with mental illness, and conversely, that genetic changes that increase PKC signaling can lead to impairments in PFC function. fMRI imaging studies of patients with bipolar disorder have already shown that lithium normalizes prefrontal activity (Blumberg et al. 2005). If more selective protein kinase C inhibitors become available for human use, it will be interesting to observe whether they are also effective in treating symptoms of PFC dysfunction such as behavioral disinhibition and distractibility, and whether they too are able to restore normal patterns of PFC activity in imaging studies.

Summary

In summary, bipolar disorder and schizophrenia are associated with profound dysfunction of the PFC and with genetic changes that disinhibit phosphatidylinositol-protein kinase C signaling. High levels of phosphatidylinositol-protein kinase C signaling in the PFC of animals markedly impair PFC regulation of thought, behavior, and emotion, and may contribute to dendritic spine loss. Most effective medications for bipolar disorder and schizophrenia inhibit phosphatidylinositol-protein kinase C signaling, either through intracellular actions (lithium, valproate) or through extracellular blockade of receptors coupled to this pathway. Recent data suggest that lithium and valproate can protect gray matter in patients with bipolar disorder. These findings encourage the development of protein kinase C inhibitors for the treatment of mental illness.

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Fig. 1. High levels of phosphatidylinositol-protein kinase C signaling in the PFC markedly impair PFC function at the behavioral and cellular levels. Molecules that normally serve as brakes on this pathway and are highly associated with genetic/biochemical alteration in mental illness are indicated in *gray*. Patients with these genetic changes would have weaker regulation of phosphatidylinositol-protein kinase C signaling. Many treatments for mental illness inhibit this signaling pathway through either extracellular or intracellular actions; these treatments are indicated in *italics*. Tamoxifen is a proof of concept (*p.o.c.*) treatment; prazosin is used to treat PTSD but not schizophrenia or bipolar disorder; chelerythrine is undergoing pre-clinical safety testing