Protein Kinase C Inhibition by Tamoxifen Antagonizes Manic-Like Behavior in Rats: Implications for the Development of Novel Therapeutics for Bipolar Disorder

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Key Words
Protein kinase C \cdot Affective disorders \cdot Depression \cdot Animal model \cdot Treatment \cdot Growth-associated protein of 43 kDa

Abstract
\textbf{Rationale:} In the context of bipolar disorder (BPD) research it was demonstrated that administration of the structurally dissimilar mood stabilizers lithium and valproate produced a striking reduction in protein kinase C (PKC) in rat brain. In a small clinical study, tamoxifen (a PKC inhibitor) had antimanic efficacy. However, both lithium and valproate exert many biochemical changes and attribution of therapeutic relevance to any molecular findings needs to be based on linking them to behavioral effects. \textbf{Objectives:} The present study was designed to explore such relationship by studying the effects of PKC inhibition in amphetamine-induced behavioral animal models of mania and changes in GAP-43. \textbf{Methods:} The effects of two daily tamoxifen (1 mg/kg) \textit{i.p.} injections on acute or chronic (7 injections) amphetamine (0.5 mg/kg) -induced behaviors and GAP-43 phosphorylation were tested. \textbf{Results:} The study demonstrates that tamoxifen significantly reduced amphetamine-induced hyperactivity in a large open field without affecting spontaneous activity levels and normalized amphetamine-induced increase in visits to the center of an open field (representing risk-taking behavior). Tamoxifen also attenuated amphetamine-induced phosphorylation of GAP-43, a result that is consistent with the behavioral findings. \textbf{Conclusions:} These results support the possibility that PKC signaling may play an important role in the pathophysiology and treatment of BPD. These findings may have direct clinical implications as they offer a new avenue for attempts to develop more specific drugs for the disorder.

Introduction

In recent years, research has increasingly investigated the role of intracellular signaling cascades in the pathophysiology and treatment of bipolar disorder (BPD) [1–4]. One signaling cascade which has received considerable interest is the protein kinase C (PKC) signaling pathway.

PKC plays a major role in regulating both pre- and postsynaptic aspects of neurotransmission [5–8]. PKC is now known to exist as a family of closely related subspe-
Table 1. Evidence implicating PKC in the pathophysiology and treatment of BPD

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It is noteworthy that psychostimulants, which are capable of triggering manic episodes in susceptible individuals [18, 19] and induce manic-like behaviors in rodents [20–22], are known to activate PKC [23–26]. Thus, the biochemical data suggests that two structurally dissimilar antimanic agents – lithium and valproate – attenuate PKC function in a therapeutically relevant time frame, while pro-manic psychostimulants activate PKC. These data suggest that PKC modulation plays a critical role in the treatment of mania. Furthermore, a small clinical study demonstrated the efficacy of tamoxifen treatment in manic patients [27]. However, the possible relationship between the PKC signaling cascade and mania has largely been investigated biochemically, without full elaboration at the behavioral level.

The present study was therefore designed to more directly assess the possible involvement of PKC inhibition with tamoxifen in manic-like behavior in animal models for mania [28, 29] and correlate these effects with biochemical change by measuring growth-associated protein of 43 kDa (GAP-43) phosphorylation. The study utilized two amphetamine-based behavioral models: hyperactivity and risk-taking behavior induced by either acute or chronic treatment. These models represent common facets of mania in patients [18]. Amphetamine-induced behavior is considered a relatively valid model for a number of reasons including similarity in behavior between the model and facets of the disease (face validity), the attenuation of amphetamine-induced behaviors by mood stabilizers (predictive validity), and the involvement of the dopaminergic system in manic behavior (construct validity) [for review see ref. 30]. Furthermore, these behaviors were tested after both acute and chronic amphetamine treatment. Tamoxifen was used in the present study to inhibit PKC because it is the only compound with documented and appreciable central nervous system PKC-inhibitory activity that can be administered peripherally and has been approved for human use [31, 32]. GAP-43 is one of the major neuronal PKC substrates. It is a common mediator of several second-messenger pathways and plays a pivotal role in neuronal differentiation, plasticity and regeneration [33].

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<td>Acute Amph GAP-43</td>
<td>Tam/Veh injection 48 h before testing</td>
<td>Tam/Veh injection 24 h before testing</td>
<td>Amphetamine/Sal injection followed 30 min later by decapitation</td>
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Amph = Amphetamine; Tam = tamoxifen; Sal = saline; Veh = vehicle.

Methods

Animals
Male Sprague-Dawley rats (CRL), n = 12 per group for acute amphetamine experiments and n = 8 per group for chronic amphetamine experiments, weighing 200–230 g at the beginning of experiments were housed, 2 per cage in an animal room with constant temperature (22 ± 1°C) and 12-hour light/dark cycle, and with free access to food and water. Rats had at least a 1-week acclimatization period in the animal room before the start of experiments. All experimental procedures were approved by the Animal Use Committee of the National Institute of Mental Health (protocol No. LMP-07-02) and were conducted according to NIH guidelines.

Drugs
The PKC inhibitor tamoxifen (Sigma, 1 mg/kg) was dissolved in propylene glycol and injected (1 ml/kg) i.p. 48 and 24 h prior to testing. The solvent, dose, timing and mode of administration were chosen based on a study showing a behavioral effect of this schedule [34].
Amphetamine sulfate (Sigma, 0.5 mg/kg) was dissolved in saline and injected i.p. (1 ml/kg) either acutely or chronically as described in the ‘Procedures’ section. The doses and timing of injections of amphetamine were chosen based on numerous studies demonstrating its behavioral effects under these schedules [35–37]. No amphetamine injections were administered during the tamoxifen treatment days and the amphetamine test injection was administered 24 h after the second tamoxifen treatment in both the acute and the chronic amphetamine studies.

Equipment
A large open field (120 × 120 cm transparent Plexiglas platform without walls, elevated 80 cm above the floor) served to study locomotor and exploratory behavior. Such large open fields were previously demonstrated to be much more effective in the study of behavior compared with the commonly used smaller activity monitors [38]. A center square of 40 × 40 cm was defined as the ‘Center’ area of the field. A video camera was placed 1.8 m above the center of the open field and interfaced with a computer and a VCR. Data were collected by the Ethovision system (Noldus Inc., Leesburg, Va., USA), a video tracking system designed to study spatial behavior.

Procedure
Timeline and Groups
The timeline for drug administration and testing is detailed in table 2. Each experiment included four groups of rats according to two factors, amphetamine treatment (yes or no) and tamoxifen treatment (yes or no).

GAP-43 Phosphorylation
Immunoblotting was conducted as previously described [16] with slight modifications. In brief, naive rats (n = 12 per group) were treated with amphetamine, tamoxifen or vehicle (table 2). Thirty minutes after the last amphetamine (or control) injection, rats were quickly decapitated, their brains were extracted and dissected on ice, and frozen in dry ice immediately (the time from decapitation to frozen samples was approximately 1 min). Frozen rat striatum was homogenized in 20 mM Tris-HCl (pH 7.5) containing 1% Triton X-100, 135 mM NaCl, 1 mM EDTA, 1 mM EGTA, 2.5 mM sodium pyrophosphate, 1 mM glycyrrehosfate, 1 mM DTT, protease inhibitor cocktail (Sigma), and phosphatase inhibitor cocktail I and II (Sigma) by passing through 18-gauge needle 5 times, 26-gauge needle 15 times followed by sonication for 10 s. The homogenates were centrifuged at 300 g for 12 min to get rid of debris. Preliminary experiments were undertaken to determine the linearity of the response for GAP-43 and phospho-GAP-43 immunoblotting with varying amounts of protein. Subsequent immunoblotting was performed using 40 μg of protein (which is within the linear range for immunoblotting). The antibodies against GAP-43 and phospho-GAP-43 were obtained from Santa Cruz Biotech (San Diego, Calif., USA) and diluted according to the manufacturer’s recommendation (1:500). The immunocomplex was detected with an Amersham Pharmacia Biotech ECL kit. Quantization of the immunoblots was performed by densitomet-

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ric scanning of the film using Kodak Image Station 440CF. Naïve rats were used for biochemical analysis because behavioral testing as well as exposure to novel environment, regardless of treatment, can induce a variety of biochemical changes. For example, locomotor activity was shown to affect the serotonergic system [39] and exposure to novelty was demonstrated to increase acetylcholine release [40]. Accordingly, since amphetamine treatment alters behavior, any results regarding biochemical changes in animals that were tested behaviorally can be attributed either to the treatment itself or to the behavioral consequences of the treatment.

Hyperlocomotion and Visits to the Center of an Open Field

Acute Amphetamine. Twenty-four hours after the second tamoxifen (or vehicle) injection, rats (n = 12 per group) were given an amphetamine (or saline) injection and singly placed in the center of the open field for a 45-min session.

Chronic Amphetamine. Rats (n = 8 per group) were treated with amphetamine (or saline) twice a week (Monday and Thursday or Tuesday and Friday) for a total of 7 injections. Tamoxifen (or vehicle) was administered 48 and 24 h prior to the last amphetamine injection. Immediately after the last injections animals were singly placed in the center of the open field for a 45-min session.

Data Analysis

Open Field. The open field experiments included four groups with a two-factors design, one factor being amphetamine treatment and the second factor being tamoxifen treatment. Analysis was conducted using a multiple factors analysis of variance (MANOVA) followed by post-hoc Scheffé tests. Two different behaviors were analyzed from the same set of data (distance traveled and center visits frequency). To overcome errors due to multiple comparisons both were analyzed together in the initial MANOVA.

Western Blot. Statistical analysis was performed by analysis of variance (ANOVA), followed by Fisher’s paired least significant difference or Scheffé’s tests.

For all analyses, p < 0.05 two-tailed test was considered significant. Data are expressed as mean ± SE.

Results

GAP-43 Phosphorylation

PKC substrate GAP-43 is phosphorylated by PKC after PKC activation [41, 42]. As shown in figure 1A, phospho-GAP-43 level increased significantly in rat striatum 30 min after amphetamine i.p. injection. Amphetamine increased phospho-GAP-43 by 40% (140 ± 14.9% of control; t = 2.42, d.f. = 22, p < 0.05), indicating that amphetamine could acutely activate PKC in vivo, consistent with a previous report [43]. Tamoxifen treatment alone did not alter phospho-GAP-43 level in the striatum, but pretreatment with tamoxifen eliminated amphetamine’s effect on GAP-43 phosphorylation (114.9 ± 13.4% of control, tamoxifen + amphetamine group not different than control). Total GAP-43 level in rat striatal homogenates did not change significantly in any treated group compared to control (fig. 1B). Having established that the tamoxifen administration paradigm attenuated the biochemical effect of amphetamine, we undertook a series of behavioral studies to investigate several facets of manic-like behavior.

Hyperlocomotion

Tamoxifen treatment reduced amphetamine-induced hyperlocomotion in the open field after both acute [total distance traveled – tamoxifen × amphetamine interaction: F(2, 10) = 6.05, p < 0.02; fig. 2A] and chronic amphetamine treatment [total distance traveled – tamoxifen × amphetamine interaction: F(2, 26) = 4.1, p = 0.03; fig. 2B] without affecting control (nonamphetamine rats) behavior. Interestingly, the locomotion levels of the amphetamine groups in the acute and chronic experiments were quite similar whereas one may expect higher locomotion in a sensitized group. However, these were separate experiments performed with different groups of animals at a different time and therefore any quantitative comparison between these experiments is not valid.

Fig. 1. Interaction between the effects of amphetamine and tamoxifen on GAP-43 phosphorylation: pretreatment with tamoxifen eliminated amphetamine’s effect on GAP-43 phosphorylation. Bars represent mean ± SE. Sal = Saline; Con = vehicle; Amp = amphetamine; Tam = tamoxifen. * p < 0.05 compared with control.
Visits to Center of Open Field
Tamoxifen treatment normalized amphetamine-induced increase in the number of visits to the center of the open field after either acute [tamoxifen × amphetamine interaction: F(2, 10) = 6.05, p < 0.02; post hoc: amphetamine different than control and than amphetamine-tamoxifen treatment; fig. 3A] or chronic [tamoxifen × amphetamine interaction: F(2, 26) = 4.1, p = 0.03; post hoc results as above; fig. 3B] amphetamine treatment.
Discussion

Abundant evidence has accumulated to show that activation of PKC enhances release of dopamine, a neurotransmitter implicated in the manic syndrome [44, 45], and that inhibition of PKC reduces amphetamine-induced dopamine release [23, 46]. Additionally, psychostimulants facilitate the release of norepinephrine and dopamine in large part by activation of PKC [23–26]. Chronic lithium and valproate attenuate PKC signaling, and their therapeutic effects in the treatment of mania are only seen after chronic administration. It was thus our working hypothesis that attenuating PKC activity not only represents a very important facet in the treatment of manic behavior, but that a direct acting PKC inhibitor would also have rapid effects.

The present study goes beyond the available data to demonstrate that tamoxifen treatment induces PKC inhibition and results in distinct behavioral changes that model antimanic effects. These effects include hyperactivity and increased risk taking, which are appropriate animal models for manic-like behaviors [20, 28, 29]. Furthermore, the attenuation of the amphetamine-induced behaviors (both acute and sensitized responses) was seen after acute administration of tamoxifen consistent with its actions as a direct acting PKC inhibitor.

Historically striatum has been considered to play a central role in the development and expression of many psychiatric disorders including schizophrenia, affective disorders, substance abuse, and attention deficit disorder. Studies in rats showed that amphetamine induced hyperactivity through reversing the dopamine transporter and increasing extracellular dopamine levels in the striatum [47], and prior depletion of dopamine in the ventral striatum could completely prevent amphetamine-induced hyperactivity. In the present study, we found that amphetamine acutely increased PKC substrate GAP-43 phosphorylation in rat striatum, and pretreatment with PKC inhibitor tamoxifen eliminated amphetamine’s effect on GAP-43 phosphorylation, paralleling with behavioral changes. These data indicate that PKC activation plays an important role in this rat mania model. We chose to use measures of GAP-43 in the present study for a few reasons: (1) GAP-43 can be phosphorylated by PKC at Ser 41 both in vitro and in vivo [48, 49]. (2) Phosphorylation of the sole PKC site in GAP-43 at Ser 41 is involved in the intracellular signal transduction pathway that regulates the structure and function of growth cones, the motile ends of growing axons, and is known to be essential for neurite elongation in primary neurons, processes that had been shown to be also related to actions of mood stabilizers [50]. (3) In PC12 cells, amphetamine-induced increases in PKC had been associated with GAP-43 changes [51]. (4) Within the hippocampus, specific changes in PKC activation and GAP-43 phosphorylation have been observed in several behavioral paradigms [52]. All in all, it appears that in the context of studying mood stabilizing effects and utilizing amphetamine-induced models, GAP-43 may be the best choice of biochemical marker for related change.

Since the present study was the first direct exploration of the affective-like behavioral effects of PKC inhibition, care was taken in the design of the study to increase the likelihood of therapeutically meaningful results: (1) the use of more than one model and of two amphetamine treatment schedules, acute and sensitized responses [20, 53]; (2) the use of a large open field rather than standard activity monitors (testing in a large environment has been demonstrated to be more sensitive to behavioral change [38]); (3) the use of a continuous, automated data collection system to reduce inaccuracies related to sampling or human errors, and (4) data analysis methods were chosen in order to correct for multiple comparisons in the open field statistics. Considering the careful design and the changes in distinct behaviors, the data suggest that acute tamoxifen treatment is able to reduce manic-like behaviors in rats.

While the behavioral and biochemical data are significant, one obvious concern is that tamoxifen is not a selective PKC inhibitor. Although tamoxifen treatment produced a reduction in GAP-43 phosphorylation, it undoubtedly also interacts with the estrogen receptor and affects other intracellular mechanisms including MAP kinases, oxidative stress, mitochondrial permeability and more [for review see ref. 54]. As mentioned above, our desire was to utilize a paradigm that could immediately have utility in human clinical studies. To the best of our knowledge, there are three compounds with PKC inhibitory activity which are approved for human use: tamoxifen [55, 56], bryostatin-I and LY-333531 [57, 58]. Extensive discussions with the National Cancer Institute (developers of bryostatin-I) suggest that this partial agonist is unlikely to cross the blood-brain barrier. There is no published data available demonstrating CNS penetration of LY-333531, and this compound is only in early clinical trials. By contrast, tamoxifen has already been used safely in women, men and children [56, 59], including for the treatment of a CNS disorder, malignant glioma [60, 61]. Furthermore, a pilot study has suggested that tamoxifen can safely be used in the treatment of acutely manic pa-
tients [27]. We therefore chose to use tamoxifen for our studies. Although we cannot exclude the possibility that estrogen receptor blockade or other intracellular effects of tamoxifen play a role in the observed behavioral changes, we think that it is unlikely for the following reasons: studies using more specific PKC inhibitors that were done in different contexts demonstrated behavioral changes that are consistent with our present results [62–67, for reviews see ref. 68, 69], and recent nonhuman primate studies investigating cognitive deficits similar to those observed in mania have also demonstrated efficacy of a selective PKC inhibitor [70]. Moreover, we did not find any studies demonstrating a specific antiestrogen effect on affective-like behavior. Estrogen itself may induce hyperactivity [71] and increased response to amphetamine [72], but these effects are not simple and may be sex-related and more prominent in females [73] while we were testing male rats. The effects may also be time-sensitive where estrogen increases amphetamine response within a short time after treatment but has a reversed effect when amphetamine testing is done 24 h after estrogen [72], while our testing was done 24 and 48 h after tamoxifen. Also, estrogen effects may be environment-dependent with no notable effects in a large open field [74] while our testing was conducted in a sizeable open field (120 × 120 cm). Taken together, while not excluding other possibilities, it is reasonable to suggest that the present effects of tamoxifen are related to its PKC-inhibitory effect and that PKC inhibition results in an antimanic-like effect in rat models of mania.

The growing appreciation that a significant percentage of patients respond poorly to existing treatments has made the task of discovering new therapeutic agents that are both efficacious and have few side effects increasingly more important. In recent years, there has been an explosion in the number of options available for the treatment of recurrent mood disorders; however, nearly all of these are more anticonvulsants or antipsychotic agents. The present study supports further exploration of PKC inhibition as a possible target for new medications. It is our contention that CNS-penetrant PKC inhibitors may not only have considerable utility in the treatment of acute mania, but may also exert their effects much more rapidly than existing medications; further investigation and possibly additional clinical trials are clearly warranted.

Acknowledgments

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