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Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania

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Abstract

There is an emerging body of data suggesting that mood disorders are associated with decreased brain-derived neurotrophic factor (BDNF). The present study aims to investigate the effects of the mood stabilizers lithium (Li) and valproate (VPT) in an animal model of bipolar disorder. In the first experiment (acute treatment), rats were administered D-amphetamine (AMPH) or saline for 14 days, and then between day 8 and 14, rats were treated with either Li, VPT or saline. In the second experiment (maintenance treatment), rats were pretreated with Li, VPT or saline, and then between day 8 and 14, rats were administered AMPH or saline. In both experiments, locomotor activity was measured using the open-field test and BDNF levels were measured in rat hippocampus by sandwich-ELISA. Li and VPT reversed AMPH-induced behavioral effects in the open-field test in both experiments. In the first experiment, Li increased BDNF levels in rat hippocampus. In the second experiment, AMPH decreased BDNF levels and Li and VPT increased BDNF levels in rat hippocampus. Our results suggest that the present model fulfills adequate face, construct and predictive validity as an animal model of mania.

Keywords: Amphetamine; Bipolar disorder; Brain-derived neurotrophic factor; Lithium; Mania; Valproate

Introduction

Bipolar disorder (BD) is a devastating major mental illness associated with higher rates of suicide and work loss (Belmaker, 2004; Kupfer, 2005). Although there have been recent advances in genetic, neurobiological and pharmacological methodologies, its pathophysiology remains largely unknown. The development of animal models has been an important tool in investigating new intracellular systems that may be involved in BD (Einat et al., 2003; Manji and Chen, 2002) and new pharmacological approaches (Lamberty et al., 2001). However, BD presents a complex alternating clinical course, with recurrent mood switches including manic, depressive, and mixed episodes, which makes the development of an adequate animal model challenging (Machado-Vieira et al., 2004). Ellenbroek and Cools (1990) have proposed that the validity of animal models in psychiatric disorders should demonstrate the following three major criteria: face, construct and predictive validity. Face validity represents how similar the model can mimic the symptoms of a determinate illness, whereas construct validity is related to the ability of the model to reproduce some pathophysiological aspects of the illness. Finally, the predictive validity evaluates if the therapeutical agents used in the treatment of an illness can reverse the symptoms induced in the animal model.

The clinical hallmark in diagnosing BD is the presence of manic symptoms (Belmaker, 2004; APA, 1994), thus an adequate animal model of BD should resemble some features of a manic episode such as euphoria, irritability, aggressiveness,

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hyperactivity, insomnia or increased sexual drive (face validity). Recent studies have demonstrated that changes in intracellular pathways that regulate neuronal transmission, plasticity and survival are associated with the pathophysiology of BD (Coyle and Duman, 2003; Bezchlibnyk and Young, 2002; Manji et al., 2001) and a reasonable animal model of bipolar disorder should both reproduce some of the molecular changes (construct validity) and response to antimanic agents, such as antipsychotics and mood stabilizers (predictive validity). A number of animal models of mania have used hyperlocomotion induced by psychostimulants (Frey et al., in press; reviewed in Machado-Vieira et al., 2004). Dopaminergic drugs, such as amphetamine, are able to induce manic symptoms in both normal human volunteers (Strakowski and Sax, 1998) and BD subjects (Anand et al., 2000). Interestingly, higher urinary dopamine levels have been associated with the emergence of manic symptoms (Joyce et al., 1995) and recent studies have demonstrated dopamine receptor changes in BD patients (Pantazopoulos et al., 2004; Vogel et al., 2004). Taken together, these studies suggest that the dopaminergic system may play a role in the pathophysiology of BD.

The pharmacological management of bipolar disorder includes the treatment of acute states and maintenance treatment in order to prevent new episodes. Mood stabilizing drugs, particularly lithium and valproate, are considered first line agents for both acute mania and maintenance treatment (Yatham et al., 2005). Several studies have suggested that the neuroprotective effects of lithium and valproate may be responsible for their therapeutical effects (Chuang et al., 2002; Li et al., 2002) and one of the mechanisms implicated is the induction of brain-derived neurotrophic factor (BDNF)/TrkB signaling pathway (Hashimoto et al., 2002; Manji et al., 2001). Recent magnetic resonance spectroscopy studies have demonstrated reduced *N*-acetyl-aspartate (a marker of neuronal viability) in the hippocampus of BD patients (Deicken et al., 2003; Bertolino et al., 2003), suggesting that BD may be associated with hippocampal dysfunction.

It is intriguing that animal models have focused primarily in the acute treatment and we are not aware of a study assessing both acute and maintenance treatments. Thus, the present study aims to investigate (a) if the administration of lithium and valproate reverses and prevents the behavioral effects of chronic use of D-amphetamine in rats, and (b) the effects of D-amphetamine and mood stabilizers on BDNF expression in rat hippocampus.

Materials and methods

Animals

The experiments were performed in male Wistar rats (age: 3–4 months; weight: 220–310 g), obtained from our breeding

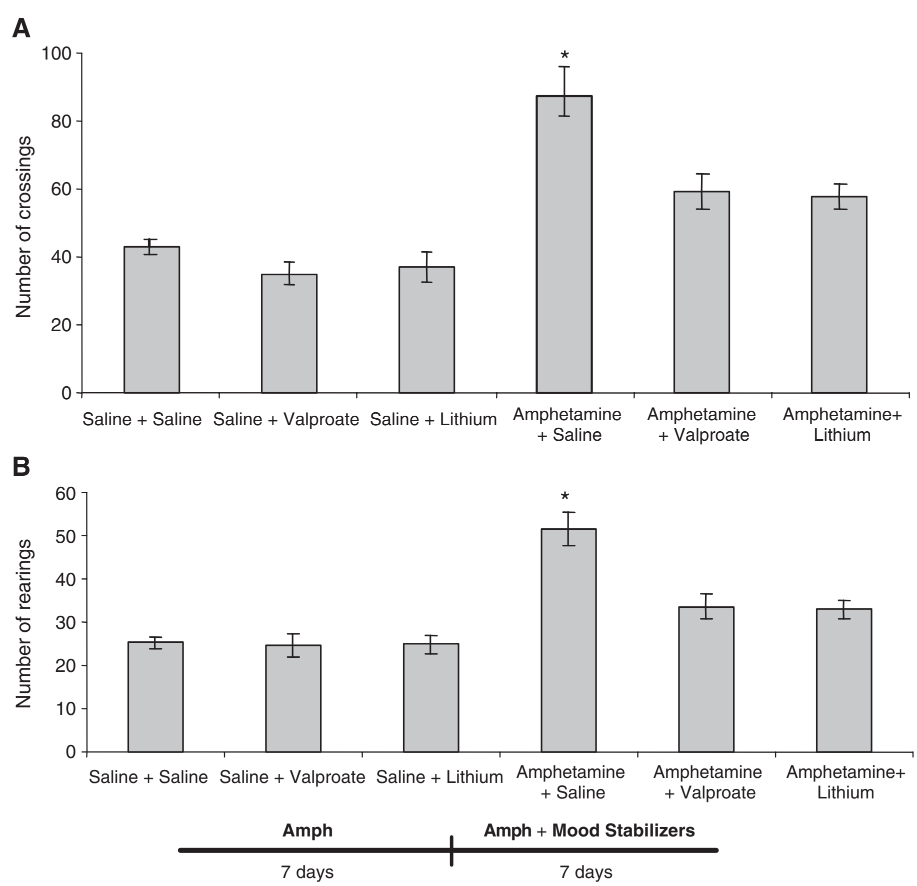

Fig. 1. Open-field test after seven days of treatment with amphetamine + seven days of amphetamine and mood stabilizers. *ANOVA and Post-test of Tukey; $p < 0.05$. Legend: Results are presented as mean ± S.E.M.

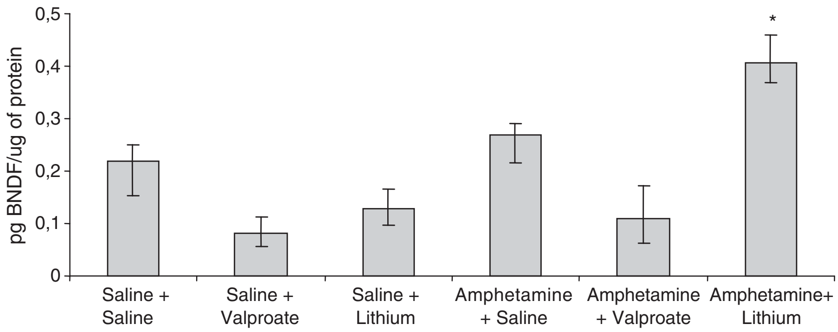

Fig. 2. Brain-derived neurotrophic factor in hippocampus after seven days of treatment with amphetamine + seven days of amphetamine and mood stabilizers. *ANOVA and Post-test of Tukey; $p<0.05$. Legend: Results are presented as mean ± S.E.M.

colony. Rats were housed five to a cage, on a 12-h light/dark cycle (lights on between 7:00 a.m. and 7:00 p.m.), and food and water were available ad libitum. All experimental procedures were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care.

Acute treatment

The first model was designed in order to reproduce the management of an acute manic episode (reversal treatment — Fig. 1). Animals received one daily IP injection of either D-amphetamine (AMPH-Sigma, St Louis, USA) 2 mg/kg or saline for 14 days (45 animals per group). Between the 8th and the 14th day, saline and AMPH animals were divided in three experimental groups (15 animals per group): lithium (Li) treatment, valproate (VPT) treatment and saline (SAL) treatment. Li-treated animals received Li 47.5 mg/kg IP twice a day, and VPT-treated animals received VPT 200 mg/kg IP twice a day. We have previously found that Li 47.5 mg/kg IP bid and valproate 200 mg/kg IP bid did not alter locomotor behavior in male Wistar rats (unpublished results). Locomotor activity was measured 2 h after the last injection, and the rats were

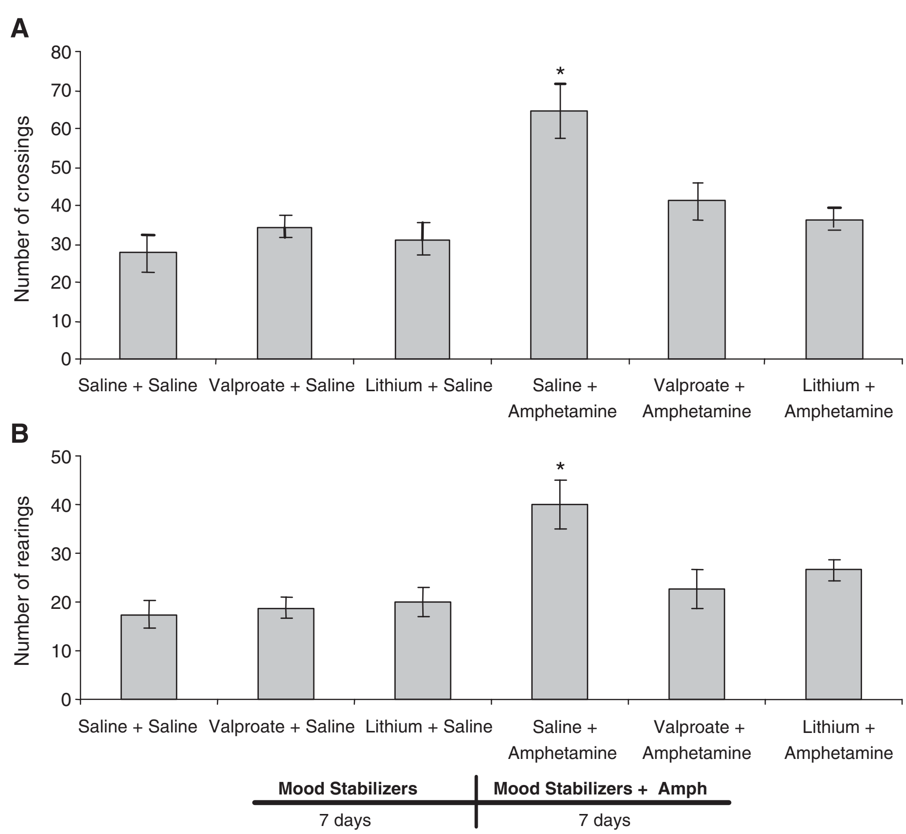

Fig. 3. Open-field test after seven days of treatment with mood stabilizers + seven days of mood stabilizers and amphetamine. *ANOVA and Post-test of Tukey; $p<0.05$. Legend: Results are presented as mean ± S.E.M.

sacrificed by decapitation right after the open-field task. The hippocampus was dissected, rapidly frozen, and stored at −80 °C until assayed.

Maintenance treatment

The second model was designed to mimic the maintenance phase of BD treatment (prevention treatment — Fig. 3). Animals received either Li 47.5 mg/kg IP twice a day, VPT 200 mg/kg IP twice a day or saline for 14 days (30 animals per group). Between the 8th and the 14th day, Li-, VPT- and saline-treated animals were divided in two experimental groups (15 animals per group): each treated group received one daily IP injection of either AMPH 2 mg/kg or saline. Locomotor activity was measured 2 h after the last injection, and the rats were sacrificed by decapitation right after the open-field task. The hippocampus was dissected, rapidly frozen, and stored at −80 °C until assayed.

Locomotor activity

The locomotor activity was assessed using the open-field task. The task was performed in a 40 × 60 cm open field surrounded by 50 cm high walls made of brown plywood with a frontal glass wall. The floor of the open field was divided into 12 equal rectangles by black lines. The animals were gently placed on the left rear quadrant, in order to explore the arena for 5 min. Crossings of the black lines and rearings were counted.

Biochemical measures

BDNF levels in hippocampus were measured by anti-BDNF sandwich-ELISA, according to the manufacturer instructions (Chemicon, USA). Briefly, brain slices were homogenized in phosphate buffer solution (PBS) with 1 mM phenylmethylsulfonyl fluoride (PMSF) and 1 mM (EGTA). Microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1 : 2 in sample diluent and standard curve ranged from 7.8 to 500 pg/ml of BNDF. The plates were then washed four times with sample diluent and a monoclonal anti-BNDF rabbit antibody diluted 1 : 1000 in sample diluent was added to each well and incubated for 3 h at room temperature. After washing, a peroxidase conjugated anti-rabbit antibody (diluted 1 : 1000) was added to each well and incubated at room temperature for 1 h. After addition of streptavidin-enzyme, substrate and stop solution, the amount of BDNF was determined by absorbance in 450 nm. The standard curve demonstrates a direct relationship between Optical Density (OD) and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin as a standard. Serum Li levels were measured by a commercial laboratory blind to the experiments.

Statistical analysis

All data are presented as mean ± S.E.M. Differences among experimental groups in experiments evaluating BNDF levels were determined by ANOVA. Multiple comparisons were performed by a Tukey test. In all experiments, p values less than 0.05 were considered to indicate statistical significance.

Results

In the first experiment (reversal treatment), AMPH increased locomotor and rearing behavior in saline-treated rats and both Li and VPT reversed AMPH-related hyperactive behavior (Fig. 1). The administration of Li or VPT in saline-treated animals did not change behavioral measures, indicating that the effects of mood stabilizers in AMPH-treated rats were not associated with sedation. AMPH administration had no effect on BDNF levels in rat hippocampus (Fig. 2). However, Li treatment increased BDNF expression after AMPH administration. VPT had no effect on BDNF levels in AMPH- or saline-pretreated animals.

Fig. 3 summarizes the behavioral measures of the second experiment (prevention treatment). Both Li and VPT pretreatment were able to prevent AMPH-related hyperactivity. Saline administration in mood stabilizer-pretreated animals demonstrated no behavioral effect. In this experiment, AMPH decreased BDNF levels in saline pretreated rats, while both Li and VPT pretreatment increased BDNF in rat hippocampus after AMPH administration (Fig. 4). Chronic use of Li and VPT in saline-treated animals had no influence in BDNF levels. Taken together, these results suggest that the effect of mood stabilizers on BDNF expression may be associated with the

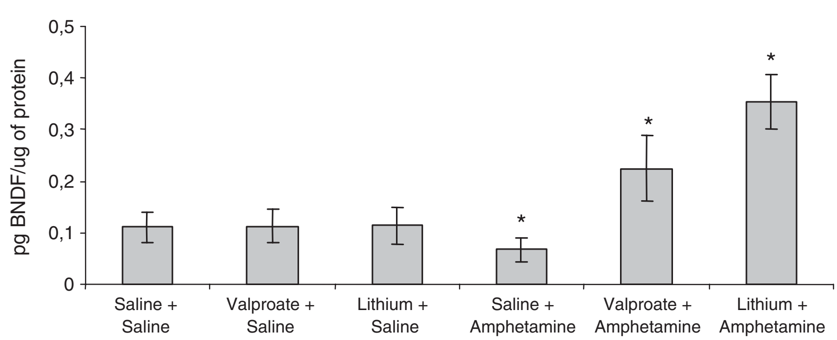

Fig. 4. Brain-derived neurotrophic factor in hippocampus after seven days of treatment with mood stabilizers + seven days of mood stabilizers and amphetamine. *ANOVA and Post-test of Tukey; $p < 0.05$. Legend: Results are presented as mean ± S.E.M.

Table 1
Serum lithium (mEq/L) in reversal and prevention experiments

Experiment/group	Serum lithium (mean-mEq/L)	S.E.M.
Reversal/saline + lithium	0.785	0.069
Reversal/amphetamine + lithium	0.772	0.053
Prevention/lithium + saline	0.926	0.088
Prevention/lithium + amphetamine	0.829	0.069

reversal and, more likely, prevention of hyperactive behavior in AMPH-treated rats. All Li-treated animals had Li plasmatic levels between 0.6 and 1.2 mEq/L (Table 1), as recommended in the treatment of BD patients.

Discussion

In the present study we investigated, for the first time, the effects of the mood stabilizing agents Li and VPT in an animal model of both acute and maintenance treatment for BD. According to our model, both mood stabilizers reversed and prevented hyperactivity induced by AMPH, indicating a good predictive validity. Despite of the well-recognized limitations of animal models of bipolar disorder in terms of face validity (Machado-Vieira et al., 2004; Einat et al., 2000), it is well known that AMPH induces manic symptoms in BD patients (Anand et al., 2000) as well as in healthy volunteers (Strakowski and Sax, 1998). Using fMRI, Bell et al. (2005) reported that Li and VPT attenuated AMPH-induced changes in human brain during neuropsychological tasks. In addition, Beaulieu et al. (2004) recently found that the hyperactivity induced by AMPH is partially mediated by Akt/glycogen synthase kinase-3β (GSK-3β) signaling pathway and that Li was able to reverse this effect. It is worth noting that both Li and VPT exert inhibitory effects over GSK-3β signaling pathway (Gould and Manji, 2002). Furthermore, it has been demonstrated that the blockade of extracellular signal-regulated kinase (ERK) pathway induces hyperactive behavior similar to that produced by AMPH (Einat et al., 2003). Interestingly, Mai et al. (2002) found that Li augmented BDNF-induced phosphorylation of ERK 1/2 in GSK-3β overexpressing cells. Thus, our findings reinforce the idea that BDNF (Narita et al., 2003; Guillin et al., 2001) and mood stabilizers (Beaulieu et al., 2004) may have adjunctive effects on the modulation of dopamine-dependent behavior.

Even though the precise pathophysiology of BD is far from being fully understood, recent studies have demonstrated that BD is associated with changes in intracellular signaling pathways that modulate neuronal plasticity and survival (Manji and Chen, 2002; Manji and Lenox, 2000). It has also been suggested that BDNF may be involved in the neurobiology of mood disorders (Duman, 2002). In the present model, we demonstrated that Li increased BDNF levels in rat hippocampus when administered both before and after AMPH, and VPT increased BDNF levels when used before AMPH (prevention treatment). This discrepancy suggests that, when co-administered with AMPH, Li may increase BDNF content in an earlier time course than VPT. We also found that neither 7 nor 14 days of administration of Li or VPT alone altered BDNF levels in rat hippocampus. Contrary to our results, Fukumoto et al. (2001) found that 14 days of Li and VPT increased BDNF expression in rat hippocampus, although they did not find changes in the expression of catalytic or truncated form of TrkB receptor. Differences in time for decapitation, dosage regimens or age of animals may account to the discrepancies between the studies. Previous studies have reported that a single administration of Li caused no significant inhibition on AMPH-induced behavioral changes (Smith, 1981; Aylmer et al., 1987; Okada et al., 1990). In addition, Aylmer et al. (1987) showed that 9 days of Li pretreatment did not inhibit AMPH-induced hyperactivity, measured on a Y-maze apparatus in female hooded rats. Differences may be due to distinct experimental design, drug dosage and animal strain used. Using in vivo microdialysis, Narita et al. (2003) demonstrated that the administration of BDNF-antibody and TrkB-antibody in the nucleus accumbens decreased dopamine release and methamphetamine-induced hyperactivity. The authors also suggested that these effects may be mediated, at least in part, by protein kinase C (PKC) modulation. In fact, several evidences have pointed out that PKC modulation seems altered in BD patients (Pandey et al., 2002; Soares et al., 2000; Wang and Friedman, 1996). In this regard, Bebchuk et al. (2000) reported significant antimanic properties of tamoxifen, a PKC inhibitor, in a small sample of manic BD patients.

Conclusion

In conclusion, we propose a new design of animal model of mania, focusing both acute and prophylactic treatments. In the present model, we were able to demonstrate that (a) the mood stabilizers Li and VPT reversed and prevented AMPH-induced hyperactivity and that (b) these effects may be associated with BDNF increase, which reinforces the notion that the neurotrophic effects of BDNF may play a role in the therapeutic effects of Li and VPT (Hashimoto et al., 2004). Studies focusing the modulation of Akt/GSK-3β and PKC signaling cascades in reversal and prevention models of BD are warranted to further clarify the molecular effects of the mood stabilizing agents.

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