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Effects of lithium and valproate on ERK/JNK signaling pathway in an animal model of mania induced by amphetamine

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ABSTRACT

Bipolar disorder (BD) is a severe and chronic psychiatric disorder, characterized by recurrent mood episodes of depression and mania. Some studies have indicated that there are ERK and JNK pathways alterations in the brain from bipolar patients. The animal model of mania induced by dextroamphetamine (d-AMPH) has been considered an excellent model to study intracellular alterations related to BD. The present study aimed to evaluate the effects of lithium (Li) and valproate (VPA) on the behavioral and ERK1/2/JNK1/2 signaling pathway in an animal model of mania induced by d-AMPH. Wistar rats were first given d-AMPH or saline (Sal) for 14 days, and then, between the 8th and 14th days, the rats were treated with Li, VPA, or Sal. The open-field test was used to evaluate the locomotion and exploration behaviors of rats. The levels of phosphorylated ERK1/2 and JNK1/2 were assessed in the hippocampus and frontal cortex of the rats. Li and VPA reversed the increased of locomotion and exploration induced by d-AMPH. The treatment with VPA or AMPH *per se* decreased the levels of pERK1 in the hippocampus. The treatment with VPA in the animals submitted to the administration of d-AMPH decreased the levels of ERK1, JNK-1, and JNK-2 phosphorylated in the hippocampus of the animals. The treatment with Li decreased the JNK-1 phosphorylated in the hippocampus of the animals submitted to the animal model of mania induced by d-AMPH. Although the association of VPA plus amphetamine alters some proteins involved in the JNK pathway in the hippocampus, these alterations were very random and seemed that were not related to the d-AMPH-induced manic-like behavior. These results suggest that the manic-like effects induced by d-AMPH and the antimanic effects of mood stabilizers, Li and VPA, are not related to the alteration on ERK1/2 and JNK1/2 pathways.

1. Introduction

Bipolar disorder (BD) is a severe and chronic condition characterized by recurrent mood episodes of depression and mania [1]. Lithium (Li) has been successfully used to treat BD and remain gold standard treatment for this disorder [2]. Besides, the anticonvulsants, such as valproate (VPA), are also used for the treatment of BD. Both mood stabilizers, Li and VPA, are useful in manic episodes and have modest antidepressant activity [3, 4]. Despite the severity of BD, little is known about the precise pathophysiology of this disorder [5]. Some theories have been made to try to elucidate the pathophysiology of BD, such as oxidative stress [6, 7, 8], the decrease of cellular plasticity and activation of cell death pathways [9, 10], which would explain the reduction of neuronal and glial density observed in bipolar patients [11, 12, 13].

The mitogen-activated protein kinases (MAPKs) are enzymes that control many cellular processes [14]. The extracellular signal-regulated kinases (ERKs) or classical mitogen-activated protein kinases (MAPKs) have an essential role in plasticity and resilience neuronal. For that

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reason, these proteins kinase have been implicated in mental disorders, such as BD, major depression, and schizophrenia [15, 16]. In a *postmortem* study with brain from bipolar patients, it was demonstrated that there are decreased levels of ERK1/2 protein in BD [17]. The c-jun amino-terminal kinases (JNKs) are MAPKs known as stress-activated proteins that are activated in response to inhibition of protein synthesis [18]. JNK also is activated by various cellular injuries, such as oxidative, mitochondrial alterations and endoplasmatic reticulum stress [19]. In this context, a previous study demonstrated that bipolar patients have higher JNK activity, which can justify the injury in the brain from this patients [20].

It is well described in the literature that brain regions involved in emotion processing are associated with mood disorders, including the prefrontal cortex [21] and hippocampus [22]. In bipolar patients, the abnormal gray matter has been showed in the frontal cortex [23]. Redlich et al. [24] also demonstrated decreased gray matter volume in the hippocampus in BD patients. In several animal models of mania, the manic-like behaviors are accompanied by biochemical and molecular alterations in frontal cortex and hippocampus of rats [25, 26].

The administration of d-amphetamine (d-AMPH) is well described in the literature as a suitable animal model of mania because it mimics some behavioral and pathophysiological characteristics observed in bipolar patients [25, 26]. In this context, the objective of the present study was to evaluate the phosphorylation of ERK1/2 and JNK1/2 in frontal cortex and hippocampus of rats submitted to the animal model induced per d-AMPH.

2. Materials and methods

2.1. Animals

Herein, it were used males Wistar rats adults (60 days old), weighing between 250-300 g, from the colony of *Universidade do Extremo Sul Catarinense*. All experimental procedures were carried out following the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC). The study was started only after the local Ethics Committee (*Comissão de Ética no Uso de Animais da Universidade do Extremo Sul Catarinense*) approved this protocol (number: 044/2016-1).

2.2. Experimental design

The animals received d-AMPH (2 mg/kg/once a day) or saline (Sal; NaCl 0.09%, 1mL/Kg/once a day) during 14 days, intraperitoneally (i.p). From the day 8^{th} until 14^{th}, the animals were treated twice a day, i.p with: Li (47.5 mg/kg); VPA (200 mg/kg) or saline (n = 10 per group). The experimental groups of the present study were: 1) Sal + Sal; 2) Sal + VPA; 3) Sal + Li; 4) d-AMPH + Sal; 5) d-AMPH + VPA; 6) d-AMPH + Li. In the 15^{th} day, the rats received d-AMPH or saline via i.p. 2h before the behavioral test.

The experimental protocol were in accordance to the Frey et al.; Kaizaki et al., Li and VPA from Jornada et al. [27, 28, 29].

2.3. Behavioral tests

The behavioral parameters were observed through the open field test. Open field test was carried out in an apparatus with 40 × 60 cm, with three 50 cm-height-walls made of wood, and the frontal wall made of glass. The floor of the apparatus had nine equal squares separated by black lines. The rats were gently put on the left posterior square to explore the area for 5 minutes. During the procedure was measured the number of crossings (locomotor activity) and rearings (exploratory activity).

2.4. Protein analysis by immunoblotting

Rats were killed by decapitation immediately after the open-field test. The frontal cortex and hippocampus from the rat's brain were then dissected, rapidly frozen, and stored at −70 °C until assayed. The samples, taken from the frontal cortex and hippocampus of the rats, were homogenized in KCl KH2PO4 (12 mM KCl, 0.038 mM KH2PO4, pH = 7.4). The frontal cortex and hippocampus were removed from the rat's brain. Brain samples were homogenized in an ice-cold lysate buffer (10 mM Tris/2 mM EDTA/200 mM NAF, protease inhibitors 0.1 mM PMSF, 2 mM Na3VO4, 1% Triton, 10% glicerol), boiled for 5 min and centrifuged at 10000 *g* for 10 min at 4 °C. One aliquot was separated to the supernatants to dosage protein, and they were stored at −20 °C up to 30 days. Protein samples were separated by SDS-PAGE, using polyacrylamide gels (10%), followed by transfer to nitrocellulose membranes using 400 mA current (3 h at 4 °C). Protein loading and blot transfer efficiency were monitored by staining with Ponceau S (0.5% Ponceau: 1% acetic acid). Membranes were blocked for 1 h with TBS-T (Tris-buffered saline and 0.1% Tween-20; pH 7.4) and fish gelatin (0.5%). Membrane blots were incubated with primary (1:1000 - Cell Signaling Technology, USA) anti-phospho-ERK1/2 (p-ERK1/2), anti-phospho-JNK1/2 (p-JNK1/2) in albumin 1%/TBS-T and incubated overnight at 4 °C. After washing, the membranes were incubated for 1 h with anti-rabbit IgG (1:1000; Santa Cruz Biotechnology, USA), or anti-rabbit IgG (1:1500; Santa Cruz Biotechnology, USA) horseradish peroxidase (HRP)-conjugated secondary antibodies, respectively. In this study was evaluated phosphorylated protein because these MAPKs achieve their biological effects through its phosphorylation. Immunocomplexes were visualized using the enhancing chemiluminescence detection system (Pierce, USA) as described by the manufacturer. Densitometry analysis were performed using Scion Image software (version beta 4.0.2; Scion Corporation, USA). The total protein concentrations were determined using the method described by Lowry et al. [30].

2.5. Statistical analysis

Results are presented as mean ± S.E.M. The variables were analyzed according to their distribution through Shapiro Wilk's test for normality. Differences among experimental groups were determined by two-way ANOVA followed by Duncan's post hoc test. A value of $p \leq 0.05$ was considered to be significant.

3. Results

Fig. 1 demonstrates that the administration of d-AMPH increased the locomotor (crossings) and exploratory (rearings) activity of animals and the treatment with Li or VPA reversed these behavioral alterations. Data from two-way ANOVA revealed significant effects of d-AMPH administration [Crossings: $F(1.54) = 108.26$, $p < 0.001$; Rearings: $F(1.54) = 27.90$, $p < 0.001$], treatment [Crossings: $F(2.54) = 36.52$, $p < 0.001$; Rearings: $F(2.54) = 21.39$, $p < 0.001$] and, a significant d-AMPH administration × treatment interaction [Crossings: $F(2.54) = 26.94$, $p < 0.001$; Rearings: $F(2.54) = 6.81$, $p < 0.05$].

Fig. 2 shows the effect of d-AMPH on phosphorylation of ERK1/2 in the frontal cortex and hippocampus of rats. The i.p. administration of d-AMPH and treatment with VPA or Li have no effects on the phosphorylation of ERK1 in the frontal cortex of rats (Fig. 2A). However, in the hippocampus, the groups Sal + VPA, d-AMPH + Sal and d-AMPH + VPA showed a decrease in the content of ERK1 phosphorylation. Data from the two-way ANOVA for d-AMPH administration [frontal cortex: $F(1.30) = 0.05$, $p = 0,823$; hippocampus: $F(1.13) = 4.84$, $p < 0.05$], treatment [frontal cortex: $F(2.30) = 0.15$, $p = 0.858$; hippocampus: $F(2.13) = 4.24$, $p < 0.05$] and, d-AMPH administration × treatment interaction [frontal cortex: $F(2.30) = 0.59$, $p = 0.556$; hippocampus: $F(2.13) = 4.46$, $p < 0.05$].

As can be observed in Fig. 2B, Li *per se* increased the ERK2

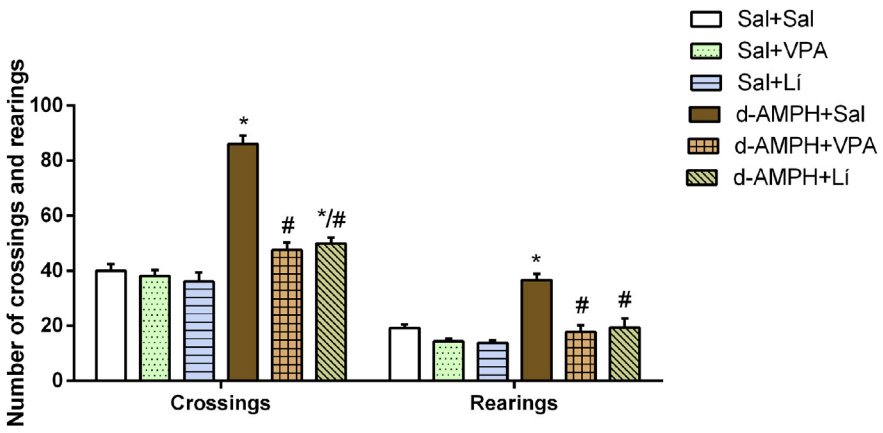

Fig. 1. Effects of administration of Li and VPA on the number of crossings and rearings of animals submitted to the d-AMPH-induced animal model (n = 10 per group). Data were analyzed by Two-ways analysis of variances followed by the Duncan test when F was significant. Values are expressed as mean ± S.E.M *p < 0.05 compared to control group. #p < 0.05 compared to d-AMPH group. d-AMPH = dextroamphetamine, Sal = Saline, Li = lithium, VPA = valproate.

phosphorylation in the frontal cortex. It was not found ERK2 alterations in the hippocampus. Data from the two-way ANOVA for d-AMPH administration [frontal cortex: F(1.26) = 0.95, p = 0,337; hippocampus: F(1.15) = 1.18, p = 0.293], treatment [frontal cortex: F(2.26) = 2.82, p = 0.077; hippocampus: F(2.15) = 1.55, p = 0.243] and, d-AMPH administration × treatment interaction [frontal cortex: F(2.26) = 0.52, p = 0.596; hippocampus: F(2.15) = 0.10, p = 0.898].

Fig. 3 shows that there is no significant result for the administration of d-AMPH *per se* on the phosphorylation of JNK1/2. It was found a decreased on JNK1 in the hippocampus of rats submitted to the d-AMPH and treated with Li or VPA (Fig. 3A). JNK1 was not altered in the frontal cortex of the rats. Data from the two-way ANOVA for d-AMPH administration [frontal cortex: F(1.12) = 4.32, p = 0.059; hippocampus: F(1.15) = 21.93, p < 0.001], treatment [frontal cortex: F(2.12) = 0.08, p = 0.917; hippocampus: F(2.15) = 4.56, p < 0.05] and, d-AMPH administration × treatment interaction [frontal cortex: F(2.12) = 1.00, p = 0.396; hippocampus: F(2.15) = 0.99, p = 0.393].

In the d-AMPH group treated with VPA was observed a decreased in the phosphorylation of JNK 2 in the hippocampus of rats (Fig. 3B). No change was observed in the frontal cortex. Data from the two-way ANOVA for d-AMPH administration [frontal cortex: F(1.12) = 5.74, p < 0.05; hippocampus: F(1.13) = 11.65, p < 0.001], treatment [frontal cortex: F(2.12) = 0.25, p = 0.782; hippocampus: F(2.13) = 0.89, p = 0.430] and, d-AMPH administration × treatment interaction [frontal cortex: F(2.12) = 1.84, p = 0.200; hippocampus: F(2.13) = 3.81, p < 0.05].

4. Discussion

It is important to emphasize that amphetamine can mimic in rats specific manic-like symptoms observed in bipolar patients, such as hyperactivity [31, 32]; for this reason, is considered a suitable animal model of mania [33, 34]. The present study demonstrated that administration of d-AMPH induced hyperactivity in rats, observed through increases of locomotor and exploratory behavior. According to our results, previous studies showed that d-AMPH induces an increase in the locomotor and exploratory activity in rodents [25, 35]. The treatment with VPA or Li reversed the alterations in locomotor and exploratory activities induced by d-AMPH in rats. Corroborating with our results, others studies demonstrated that treatment with Li and VPA reversed the hyperlocomotion induced by d-AMPH [25, 36].

The previous clinical study has demonstrated that T cells of BD patients had increased p-ERK signaling [37, 38]. Besides, a previous clinical study showed that JNK levels were significantly higher in bipolar patients than in healthy controls upon drug stimulation, especially with escitalopram stimulation [20]. Therefore, the present study hypothesized that the MAPKs signaling pathway changes could accompany the manic-like symptoms induced by d-AMPH. However, the present study demonstrated that d-AMPH administration decreased ERK1 phosphorylation in the hippocampus, but no alteration was observed in ERK2 phosphorylation. Llorente-Berzal and colleagues [39] found a reduction in ERK1/2 immunoreactivity in the frontal cortex of the male rats treated with 3,4-methylenedioxymethamphetamine. In contrast, Shi and McGinty [40] showed that AMPH-pretreated rats had phospho-ERK significantly elevated in the striatum. In another study of Hebert and O'Callaghan [41], it was also observed an increase of ERK1/2 phosphorylation after six hours of administration the methamphetamine. It seems that, after AMPH administration, ERK1/2 proteins are translocated to the nucleus, which induces phosphorylation and activation of transcription factors, such as CREB [42]. This discrepancy could be explained, at least in part, by methodological differences between our and the previous study. In the research of Shi and McGintythe [30], for example, the dose of AMPH was 5 mg/kg, and the animals were evaluated two weeks after the last administration of AMPH administered.

In the present study, d-AMPH did not change the phosphorylation of JNK in the brain of rats. The role of JNK signaling AMPH-induced neuronal damage has been poorly investigated; however, a preclinical study demonstrated that a single high dose of methamphetamine induces extensive apoptosis in the mouse brain, through JNK signaling [43]. Besides, Urrutia and colleagues [44] showed that JNK inhibition

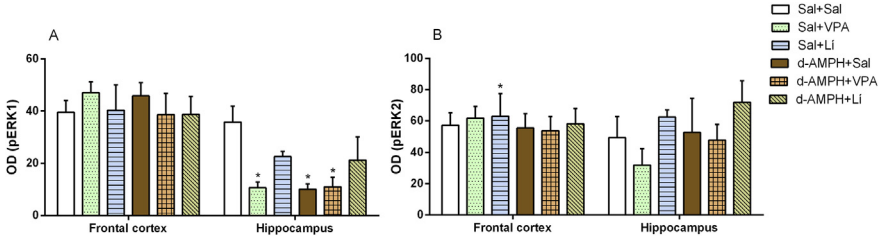

Fig. 2. Effects of administration of Li and VPA on the phosphorylation of ERK1 (A) and ERK2 (B) in the frontal cortex, and hippocampus of animals submitted to the d-AMPH-induced animal model (n = 10 per group). Data were analyzed by Two-ways analysis of variances followed by the Duncan test when F was significant. Values are expressed as mean ± S.E.M *p < 0.05 compared to the control group. #p < 0.05 compared to d-AMPH group. d-AMPH = dextroamphetamine, Sal = Saline, Li = lithium, VPA = valproate.

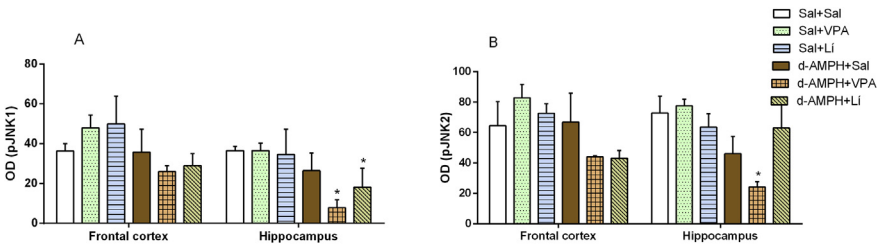

Fig. 3. Effects of administration of Li and VPA on the phosphorylation of JNK1 (A) and JNK2 (B) in the frontal cortex, and hippocampus of animals submitted to d-AMPH-induced animal model (n = 10 per group). Data were analyzed by Two-ways analysis of variances followed by the Duncan test when F was significant. Values are expressed as mean ± S.E.M *p < 0.05 compared to control group. #p < 0.05 compared to the d-AMPH group. d-AMPH = dextroamphetamine, Sal = Saline, Li = lithium, VPA = valproate.

prevented methamphetamine-induced changes in matrix metalloproteinase activity, laminin degradation, and blood-brain barrier leakage. This discrepancy could be explained, at least in part, by methodological differences between our and the previous study. More studies are needed to elucidate the effects of amphetamines on cerebral JNK better.

About the effects of mood stabilizers on MAPKs, VPA decreased hippocampal ERK1 phosphorylation in both saline or d-AMPH treated rats. It can also be observed that VPA also reduced JNK1/2 phosphorylation in the hippocampus of rats pretreated with d-AMPH. However, Zhang and colleagues [45] demonstrated that 1-methyl-4-phenylpyridinium (MPP+)-treatment decreased ERK phosphorylation and VPA reversed this effect, protecting dopaminergic neurons from MPP + -induced neurotoxicity [45]. On the other hand, a previous study has shown that VPA has no effects on microglial ERK and JNK [46]. Chen and colleagues [47] also did not find phosphorylation of ERK1/2 and JNK from lymphocytes after VPA treatment. Together with our data, these studies suggest that the effects of VPA may depend on the cell and dosages used in different studies.

In the present study, Li per se increased the phosphorylation of ERK2 in the frontal cortex of animals. Besides, Li treatment decreased JNK in the hippocampus of d-AMPH-treated rats. Xia and colleagues [48] have demonstrated that Li protects the brain against phencyclidine-induced neurotoxicity by increasing phosphorylation of ERK, Akt, and GSK-3. Also, the previous pre-clinical study showed that Li regulates hippocampal neurogenesis after transient global cerebral ischemia by increased of ERK phosphorylation [49]. Several clinical and preclinical studies have demonstrated that Li increased ERK phosphorylation [50, 51]. About JNK, it is well also described in the literature that Li inhibit this protein, protecting the brain against cellular apoptosis [52]. The previous study demonstrated that long-term treatment with Li suppresses glutamate-induced JNK activation in cultured brain neurons [53].

It is well described that VPA and Li activate the lipid kinase phosphatidylinositol 3-kinase (PI3K), protein kinase B (PKB)/Akt and the mitogen-activated protein kinases (MAPKs). The PI3K/Akt signaling pathway plays an essential role in neuronal survival and neuroprotection [54]. VPA and Li cause an upregulation of Akt activation via phosphorylation mediated by the PI3K pathway in both in vitro and in vivo models. MAPK is an important signal transduction pathway involved in neuronal survival. In this way, the mood stabilizers activate extracellular signal-regulated kinases (ERKs) and promote neurotrophic effects [55, 56, 57, 58]. In contrast, JNK is a proapoptotic molecule, and its inhibition has been suggested to cause neuroprotective and antioxidative effects [52, 59]. Therefore, some studies have demonstrated that mood stabilizers, Li and VPA, act on this molecule inhibiting its action on the brain [52]. In this study, in a general view, both VPA and Li did not change the MAPK pathway importantly but reversed the manic-like behavior. These mood stabilizers have many other action mechanisms that explain its therapeutical effects, such as glycogen synthase kinase-3, protein kinase C and neurotrophins [58, 60, 61].

In conclusion, the present study showed that: 1) d-AMPH decreased ERK1 phosphorylation in the hippocampus; 2) VPA decreased hippocampal ERK1 phosphorylation in both saline or d-AMPH treated rats; 3) VPA reduced JNK1/2 phosphorylation in the hippocampus of rats pretreated with d-AMPH; 4) Li per se increased the phosphorylation of ERK2 in the frontal cortex of animals and; 5) Li treatment decreased JNK in the hippocampus of d-AMPH-treated rats. Although amphetamine and mood stabilizers act on MAPK signaling pathway, these effects were dependent on treatment and assessed brain structure. In general, it seems that the manic-like behavior induced by d-AMPH and the antimanic effects of mood stabilizers were not accompanied by a standard effect on the MAPK pathway. Li and VPA have many other action mechanisms that explain its therapeutical effects; therefore, we suggest that the antimanic effects of these stabilizers, in the present study, are not linked to the MAPK signaling pathway.

Declarations

Author contribution statement

Samira S. Valvassori, Carina Rodrigues Boeck, Mônica Levy Andersen, João Quevedo: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Fernanda F. Gava, Gustavo C. Dal-Pont: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Henio Leonardo Simões, Marcela Damiani-Neves: Performed the experiments.

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Competing interest statement

The authors declare the following conflict of interests:

João Quevedo;

I. Clinical Research Support: Janssen Pharmaceutical (Clinical Trial), Allergan (Clinical Trial)

II. Advisory Boards, Speaker Bureaus, Expert Witness, or Consultant: Daiichi Sankyo (Speaker Bureau)

III. Patent, Equity, or Royalty: Instituto de Neurociencias Dr. Joao Quevedo (Stockholder)

IV. Other: Artmed Editora (Copyright), Artmed Panamericana (Copyright).

Additional information

No additional information is available for this paper.

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