Journal of Psychiatric Research 45 (2011) 162–168

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Lithium and valproate modulate antioxidant enzymes and prevent ouabain-induced oxidative damage in an animal model of mania

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ARTICLE INFO

Article history:
Received 18 February 2010
Received in revised form
4 May 2010
Accepted 7 May 2010

Keywords:
Ouabain
Mania
Oxidative stress
Submitochondrial particles
Lithium
Valproate

ABSTRACT

In this study, we assessed the oxidative stress parameters in rats submitted to an animal model of mania induced by ouabain (OUA), which included the use of lithium (Li) and valproate (VPA). Li and VPA treatment reversed and prevented the OUA-induced damage in these structures, however, this effect varies depending on the brain region and treatment regimen. Moreover, the activity of the antioxidant enzymes, namely, superoxide dismutase (SOD) and catalase (CAT) was found to be increased and decreased, respectively, in the brain of OUA-administered rats. Li and VPA modulated SOD and CAT activities in OUA-subjected rats in both experimental models. Our results support the notion that Li and VPA exert antioxidant-like properties in the brain of rats submitted to animal model of mania induced by ouabain.

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1. Introduction

Bipolar disorder (BD) is a prevalent and chronic psychiatric disorder (Belmaker, 2004). It is considered to be one of the leading causes of disability among all medical and psychiatric conditions (Murray and Lopez, 1997), and untreated BD has been associated with increased morbidity and mortality due to general medical conditions such as vascular disorders and cancer (Angst et al., 2002).

Oxidative stress mechanisms have been implicated in the pathogenesis of psychiatric disorder such as bipolar disorder (Halliwell, 2006). Aerobic organisms are susceptible to oxidative stress because semi-reduced oxygen species, superoxide and hydrogen peroxide are produced by mitochondria during respiration (Chance et al., 1979). The brain is particularly vulnerable to reactive oxygen species production because it metabolizes 20% of total body oxygen and has a limited amount of antioxidant capacity (Floyd, 1999), and in fact early studies demonstrating the ease of brain membrane peroxidation supported this notion (Zaleska and Floyd, 1985).

The primary antioxidant defense system has been studied in several psychiatric disorders and involves coordinated effects induced by superoxide dismutase (SOD) and catalase (CAT) (Reddy et al., 1991; Kapczinski et al., 2008). SOD is a protective enzyme that can selectively scavenge the superoxide anion radical (O_2^-) by catalyzing its dismutation to hydrogen peroxide (H_2O_2) and CAT metabolizes the excess of H_2O_2 producing $O_2 + H_2O$, decreasing the intracellular redox status (Andreazza et al., 2008a).

Moreover, the role of Na^+/K^+-ATPase in the pathophysiology of bipolar disorder was reported by El-Mallakh et al. (2003). The pharmacological inhibition of Na^+/K^+-ATPase by ouabain in rats causes hyperactivity and can be used as a model of mania (El-Mallakh et al., 2003; Li et al., 1997; Decker et al., 2000). Riegel et al. (2009) found that mania-like state induced by ouabain increased superoxide generation and lipid peroxidation in submitochondrial particles of the rat brain, suggesting that the decrease in the activity of Na^+/K^+-ATPase seen in bipolar patients may be an important link in the pathological response to oxidative stress.

Mood stabilizing drugs, particularly lithium and valproate, are considered as first-line agents for both acute mania and

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doi:10.1016/j.jpsychires.2010.05.011

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., 1997). Recently a study of our laboratory demonstrated that Li and VPA reversed OUA-related hyperactive behavior in the open-field test, suggesting that this model fulfills adequate face, construct and predictive validity as an animal model of mania (Jornada et al., 2009).

In this context, we sought to investigate the effects of lithium and valproate on oxidative stress parameters in the brain of rats using an animal model of mania induced by ouabain.

2. Experimental methods

In the present study, we have extended the investigation of the effects of Li and VPA on ouabain-induced neurochemical alterations in an animal model of mania by measuring oxidative stress parameters in prefrontal and hippocampal samples that were kept frozen at −80 °C from one of our previous experiments (Jornada et al., 2009). The detailed description of the experiments has been published elsewhere (Jornada et al., 2009); therefore, we summarize here the treatment regimens and describe the subsequent steps performed for the present investigation.

2.1. Animals

The subjects were adult male Wistar rats (weighing 250–350 g) obtained from our breeding colony. Animals were housed five to a cage with food and water available ad libitum and were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.) at a temperature of 22 ± 1 °C. All experimental procedures were performed in accordance with the approval of the local Ethics Committee. All experiments were performed at the same time during the day to avoid circadian variations.

2.2. Surgical procedure

Animals were intraperitoneally anesthetized with ketamine (80 mg/kg) and xylazine (10 mg/kg). In a stereotaxic apparatus, the skin of the rat skull was removed and a 27-gauge 9 mm guide cannula was placed at 0.9 mm posterior to bregma, 1.5 mm right from the midline and 1.0 mm above the lateral brain ventricle. Through a 2-mm hole made at the cranial bone, a cannula was implanted 2.6 mm ventral to the superior surface of the skull and fixed with dental acrylic cement. Animals recovered from surgery within 3 days.

2.3. Treatment

Reversal model: We designed our first model to reproduce the management of an acute manic episode. Animals (n = 72) received a single ICV injection of 5 μl of 10^{-3} M ouabain dissolved in artificial cerebrospinal fluid (ACSF) or 5 μl of ACSF alone on the fourth day following surgery (El-Mallakh et al., 2003; Riegel et al., 2009). (Note: Hamid et al. (2009) published reports in which the ouabain dose was reported as 10^{-5} M are in error; the dose used in those studies was 10^{-3} M.) A 30-gauge cannula was placed inside the guide cannula and connected by a polyethylene tube to a microsyringe. The tip of the cannula infusion protruded 1.0 mm beyond the cannula guide aiming the right lateral brain ventricle. From the day following the injection of ouabain or ACSF, the rats were treated for 6 days with intraperitoneal (IP) injections of saline, lithium or valproate in 6 experimental groups of 12 animals per group: ACSF ICV + saline IP (ACSF + Sal), ACSF ICV + lithium IP (ACSF + Li), ACSF ICV + valproate IP (ACSF + VPA), ouabain ICV + saline IP (OUA + Sal), ouabain ICV + lithium IP (OUA + Li), ouabain ICV + valproate IP (OUA + VPA). Animals in the Li group received intraperitoneal injections of lithium (47.5 mg/kg) and those in the VPA group received valproate (200 mg/kg) twice a day (Jornada et al., 2009). The animals were killed 24 h after the last injection of Li, VPA or ACSF.

Maintenance model: We designed the second model to mimic the maintenance phase of the treatment of BD, when the drugs still are administered even in periods of euthymia (prevention model). After recovery from surgery, animals (n = 72) received IP injections of Li (47.5 mg/kg), VPA (200 mg/kg) or SAL twice a day for 12 days. In the 7 days of treatment with Sal, Li or VPA the animals received a single ICV injection of either OUA (10^{-3} M) or ACSF, totaling 6 experimental groups of 12 animals per group: Sal - + ACSF, Li + ACSF, VPA + ACSF, Sal + OUA, Li + OUA, VPA - + OUA. After the OUA or ACSF injection, the treatment with mood stabilizer was continued for 6 more days (Jornada et al., 2009). The animals were killed 24 h after the last injection of Li, VPA or ACSF.

2.4. Biochemical analysis

Rats were sacrificed by decapitation and the brain transferred within 1 min to ice-cold isolation buffer (0.23 M mannitol, 0.07 M sucrose, 10 mM Tris–HCl, and 1 mM EDTA, pH 7.4). The prefrontal cortex and hippocampus (n = 5 animals per group) were dissected in ice-cold buffer in a Petri dish, and submitochondrial particles were prepared in parallel from the four brain regions of each animal. For biochemical analysis in total tissue, the brain structures were rapidly frozen and stored at −80 °C.

2.5. Mitochondrial isolation

Rat brain homogenates were centrifuged at 700 g for 10 min to discard nuclei and cell debris and the pellet was washed to enrich the supernatant that was centrifuged at 7000 g for 10 min. The obtained pellet, washed and resuspended in the same buffer, was considered to consist mainly of intact mitochondria able to carry out oxidative phosphorylation. The operations were carried out at 0–2 °C. Submitochondrial particles (SMP) were obtained by freezing and thawing (three times) of isolated mitochondria. For superoxide production measurements, SMP were washed twice with 140 mM KCl, 20 mM Tris–HCl (pH 7.4) and suspended in the same medium (Boveris et al., 1972).

2.6. Superoxide production in submitochondrial particles of the rat brain

Superoxide production was determined in washed brain SMP using a spectrophotometric assay based on superoxide-dependent oxidation of epinephrine to adrenochrome at 37 °C ($\lambda_{480\ nm}$ = 4.0 $mM^{-1}\ cm^{-1}$). The reaction medium consisted of 0.23 M mannitol, 0.07 M sucrose, 20 mM Tris–HCl (pH 7.4), SMP (0.3–1.0 mg protein/ml), 0.1 μM catalase, and 1 mM epinephrine. NADH (50 μM) and succinate (7 mM) were used as substrates and rotenone (1 μM) and antimycin (1 μM) were added as specific inhibitors, respectively, to assay O_2^- production at the NADH dehydrogenase and at the ubiquinone–cytochrome b region. Superoxide dismutase (SOD) was used at 0.1–0.3 μM final concentration to give assay specificity (Boveris, 1984).

2.7. Thiobarbituric acid reactive species (TBARS) content in tissue and in submitochondrial particles of the rat brain

As a marker of lipid peroxidation, we measured the formation of thiobarbituric acid reactive species (TBARS) during an acid-heating

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