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Sodium butyrate has an antimanic effect and protects the brain against oxidative stress in an animal model of mania induced by ouabain

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ABSTRACT

Studies have consistently reported the participation of oxidative stress in bipolar disorder (BD). Evidence indicates that epigenetic regulations have been implicated in the pathophysiology of mood disorders. Considering these evidences, the present study aimed to investigate the effects of sodium butyrate (SB), a histone deacetylase (HDAC)inhibitor, on manic-like behavior and oxidative stress parameters (TBARS and protein carbonyl content and SOD and CAT activities) in frontal cortex and hippocampus of rats subjected to the animal model of mania induced by intracerebroventricular (ICV) ouabain administration.The results showed that SB reversed ouabain-induced hyperactivity, which represents a manic-like behavior in rats. In addition, the ouabain ICV administration induced oxidative damage to lipid and protein and alters antioxidant enzymes activity in all brain structures analyzed. The treatment with SB was able to reversesboth behavioral and oxidative stress parameters alteration induced by ouabain.In conclusion, we suggest that SB can be considered a potential new mood stabilizer by acts on manic-like behavior and regulatesthe antioxidant enzyme activities, protecting the brain against oxidative damage.

1. Introduction

Bipolar disorder (BD) is a chronic, severe and prevalent psychiatric disorder with recurrent mood changes. BD is characterized by at least one manic episode, with alternations between depressive, manic, and mixed episodes (Zarate et al., 2006). The pharmacological management of BD includes the treatment of acute states and maintenance treatment to prevent new episodes. Lithium and valproate are considered first-line agents for both acute mania and maintenance treatment (Yatham et al., 2013). However, a large number of bipolar patients do not respond adequately to these medications and experience a range of side effects, which leads to poor adherence to the medication (Lund et al., 2012).

Evidences indicate that epigenetic regulations have been implicated in the pathophysiology of mood disorders (Resende et al., 2013; Valvassori et al., 2013; Peedicayil 2014). In fact, one of the valproate (a drug widely used on BD treatment) action mechanisms is the inhibition of histones deacetylase (Phiel et al., 2001). Recently, preclinical studies from our research group and others have demonstrated that histone deacetylase (HDAC) inhibitors, such as sodium butyrate (SB), can act as mood stabilizers, reversing manic- and depressive-like behavior in animal models of mania and depression, respectively (Schroeder et al., 2007; Moretti et al., 2011; Resende et al., 2013; Valvassori et al., 2013). HDAC inhibitors act on chromatin structure, facilitating gene expression, and studies have suggested that the therapeutic effects of these substances may be related to the increased expression of proteins involved in neuronal synaptic plasticity (Gurvich et al., 2005; Arent et al., 2011; Machado-Vieira et al., 2004; Resende et al., 2013). However, little is known about the specific therapeutic effects of HDAC inhibitors.

Even though the biologic basis of BD remains unknown, studies have shown that mitochondrial dysfunction, oxidative stress, and cellular oxidative damage are related to this mood disorder

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(Steckert et al., 2010; Clay et al., 2011; Gigante et al., 2011). Oxidative stress occurs in aerobic organisms because of the production of reactive oxygen species (ROS), which takes place primarily in mitochondria via the respiratory chain. Oxidative stress is characterized by an imbalance between reactive oxygen species, which are responsible for the production of free radicals and antioxidants. Studies have shown that the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) are the most important enzymes involved in psychiatric disorders (Kapczinski et al., 2008; Reddy et al., 1990). SOD is a protective enzyme that can selectively remove superoxide anion radicals by catalyzing the dismutation of hydrogen peroxide (H_2O_2); in turn, CAT metabolizes excessively produced H_2O_2 by converting it to O_2+H_2O (Halliwell, 2006).

Intracerebroventricular (ICV) injection of ouabain induces hyperactivity in rats by inhibiting the Na+/K+ −ATPase and, consequently increases in intracellular calcium levels (El-Mallakh and Wyatt, 1995). Interestingly, these alterations are also seen in brain from bipolar patients (Banerjee et al., 2012; Dubovsky et al., 2014), suggesting that ouabain model is a relevant animal model of mania. (Machado-Vieira et al., 2004; Young et al., 2011). Studies of this animal model have shown that manic-like hyperactivity induced by ouabain is associated with similar brain alterations seen on BD clinic and increased formation of lipid and protein oxidation products in the prefrontal cortex and hippocampus of rats (Riegel et al., 2009; Jornada et al., 2011). In addition, previous studies from our laboratory have demonstrated that SB reverses the ouabain-induced hyperactivity and mitochondrial alterations in the brains of rats (Resende et al., 2013; Valvassori et al., 2013).

To continue studying the effects of SB, we designed the present study to investigate the effects of SB administration on behavioral and oxidative stress parameters (TBARS and protein carbonyl content and SOD and CAT activity) in the frontal cortex and hippocampus of rats subjected to the animal model of mania induced by ouabain.

2. Methods

2.1. Animals

We conducted the study using adult male *Wistar* rats obtained from our breeding colony. The animals were housed 5 to a cage, on a 12-h light/dark cycle (lights on at 7:00 am), with free access to food and water. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC). This study was approved by the local ethics committe (Comitê de Ética no Uso de Animais da Universidade do ExtremoSulCatarinense), and all efforts were made to minimize animal suffering.

2.2. Animal model of mania induced by ouabain

Animals were intramuscularly 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 the 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 above the ventral to the superior surface of the skull, and fixed with jeweler acrylic cement. Animals recovered from surgery in 3 days.

Note: Postmortem verification of cannula placements was performed as described in previous papers (Barros et al., 1999). Brains were verified by histological examination, in 33% of animals in each group. In all analyzed animals the cannula was correctly placed (Fig. 1).

We designed this model to reproduce the management of an acute manic episode. Animals (n=40) received a single ICV injection of 5 μL of ouabain 10^{-3} M dissolved in artificial cerebrospinal fluid [(aCSF) 145 mM NaCly 2.7 mM KCly1.0 mM MgCl2y2.0 mM NaH2PO4, pH 7.4], or 5 μL of aCSF alone, on the 4th day following surgery (El-Mallakh et al., 2003; Riegel et al., 2009). A 30 gauge cannula was placed into 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 at the right lateral brain ventricle. From the day following the injection of ouabain or aCSF, the rats were treated for six days with i.p. injections of Sal or SB, into four experimental groups of 10 animals per group: aCSF ICV+saline i.p. (aCSF+Sal), aCSF ICV+SB i.p. (aCSF+SB), ouabain ICV+saline i.p. (OUA+Sal), ouabain ICV+SB i.p. (OUA+SB). Animals in the SB group received SB (500 mg/kg) twice a day. We measured locomotor activity, in the open-field test, 7 days after ouabain administration, the day following the end of treatment with SB or Sal.

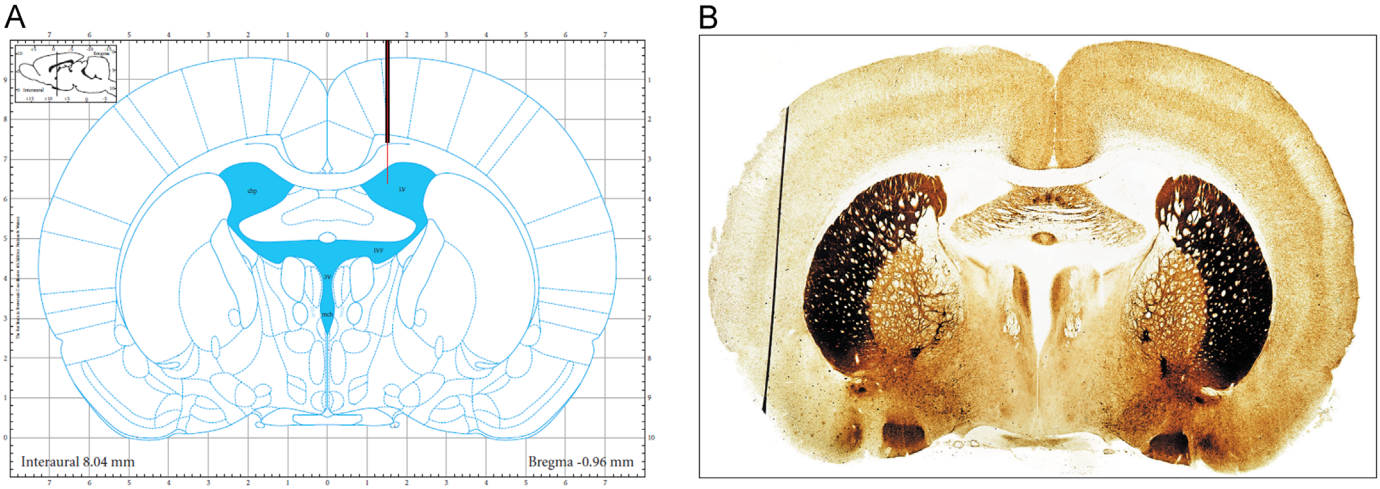

Fig. 1. Histological ICV injection. **A:** Schematic representation of brain region injected. Black vertical line represents guide cannula implanted during stereotaxic surgery and red line represents the needle infusion on lateral ventricle. **B:** Brain plate of ventricle areas. LV= Lateral Ventricle; IVF= Intraventricular foramen; 3 V= 3 rd Ventricle, mch=medial corticohypothalamic tract; chp= choroid plexus. Figure modified from Paxinos and Watson (2006).