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Electroencephalographic study of chlorpromazine alone or combined with alpha-lipoic acid in a model of schizophrenia induced by ketamine in rats

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ABSTRACT

Schizophrenia is characterized by behavioral symptoms, brain function impairments and electroencephalographic (EEG) changes. Dysregulation of immune responses and oxidative imbalance underpins this mental disorder. The present study aimed to investigate the effects of the typical antipsychotic chlorpromazine (CP) alone or combined with the natural antioxidant alpha-lipoic acid (ALA) on changes in the hippocampal average spectral power induced by ketamine (KET). Three days after stereotactic implantation of electrodes, male Wistar rats were divided into groups treated for 10 days with saline (control) or KET (10 mg/kg, IP). CP (1 or 5 mg/kg, IP) alone or combined with ALA (100 mg/kg, P.O.) was administered 30 min before KET or saline. Hippocampal EEG recordings were taken on the 1st, 5th and 10th days of treatment immediately after the last drug administration. KET significantly increased average spectral power of delta and gamma-high bands on the 5th and 10th days of treatment when compared to control. Gamma low-band significantly increased on the 1st, 5th and 10th days when compared to control group. This effect of KET was prevented by CP alone or combined with ALA. Indeed, the combination of ALA 100 + CP1 potentiated the inhibitory effects of CP1 on gamma low-band oscillations. In conclusion, our results showed that KET presents excitatory and time-dependent effects on hippocampal EEG bands activity. KET excitatory effects on EEG were prevented by CP alone and in some situations potentiated by its combination with ALA.

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1. Introduction

Schizophrenia is a neuropsychiatric syndrome characterized by impairment of brain functions such as language, thought processing, memory and cognition (WHO, 2015; Moore et al., 2015; Berberian et al., 2015). The syndrome is characterized by the occurrence of symptoms divided into: positive (psychotic period, i.e. presence of abnormal behaviors such as delusions, paranoia, visual and auditory hallucinations, disordered and incoherent thoughts and loss of normal association between ideas), negative (absence of interpersonal and social behaviors often chronic and difficult to treat, such as social withdrawal, apathy and anhedonia) and cognitive symptoms (Meyer and Feldon, 2010).

Patients with schizophrenia, in addition to presenting behavioral symptoms, also show electroencephalographic (EEG) changes especially during crises (Dawson et al., 2015). These altered

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electrical activities are related to the malfunction of brain structures like the hippocampus, amygdala, thalamus, temporal and frontal cortex (Kandratavicius et al., 2012).

Ketamine (KET), a non-competitive antagonist of N-methyl-D-aspartate (NMDA) glutamate receptor, is clinically used as an anesthetic when in high doses (160 mg/kg) (Yilmaz et al., 2002). However, non-anesthetic doses of KET in rodents [10 mg/kg (De Oliveira Viana Arruda et al., 2008); 20 mg/kg (Vasconcelos et al., 2015; Monte et al., 2013); 25, 50 or 75 mg/kg (Caixeta et al., 2013), and 100 mg/kg (Moghaddam et al., 2014)] induce cognitive impairment, psychosis and exacerbation of schizophrenic-like symptoms. Based on these evidences, KET is widely used as an animal model of schizophrenia (Vasconcelos et al., 2015; Monte et al., 2013; Moghaddam et al., 2014; Chatterjee et al., 2011; De Oliveira Viana Arruda et al., 2008). Several studies (Newcomer et al., 1999; Stone et al., 2006; Kim et al., 2015) showed that a single dose of KET induces a state in the brain characterized by an increase in the force and frequency of cerebral intrinsic oscillations. Spectral analysis revealed an increase in the absolute power after administration of 9 or 30 mg/kg doses of KET, with the greatest increase being achieved on delta-, beta- and gamma-bands. These changes were more prominent 10–15 min after KET administration, which temporally correlates with the higher levels of KET and its metabolite, norketamine, in the brain (Páleníček et al., 2011).

Antipsychotics, drugs used to treat schizophrenia, are grouped into typical and atypical. Both typical and atypical antipsychotics appear to be equally effective for the treatment of positive symptoms of schizophrenia, by inhibiting the mesolimbic dopaminergic system. However, atypical antipsychotics seems to be more effective in treating the negative symptoms and cognitive impairment (Keefe et al., 2007). Like other typical antipsychotics, chlorpromazine (CP) selectively blocks dopamine D2 postsynaptic receptors (Peuskens et al., 2014), which seems to be related to the occurrence of important side effects such as tardive dyskinesia and EEG abnormalities (Momcilović-Kostadinović et al., 2013; Erbas and Yilmaz, 2013; Fink, 2010).

Besides from the involvement of neurotransmitters in the pathophysiology of psychiatric disorders, in the last decades the contribution of chronic inflammation in the neurobiology of these disorders has received increased attention (Fond et al., 2014). In this regard, previous studies have shown that schizophrenia is associated with a dysregulation of immune responses (Drexhage et al., 2011; Miller et al., 2013; (Potvin et al., 2008) and oxidative imbalance (Koga et al., 2015; Macêdo et al., 2012). Furthermore, some anti-inflammatory drugs have shown effectiveness in the treatment of schizophrenia (Koga et al., 2015; Macêdo et al., 2012).

Due to its strong antioxidant and anti-inflammatory effects, the therapeutic potential of alpha-lipoic acid (ALA) has been recently studied for neuropsychiatric disorders (Silva et al., 2016; Sousa et al., 2015; Vasconcelos et al., 2015; Deslauriers et al., 2014; Silva et al., 2014, 2013; De Araújo et al., 2011). Thus, considering that schizophrenia has oxidative and inflammatory components underlying its pathophysiology, ALA has been investigated as a therapeutic alternative for schizophrenia (Vasconcelos et al., 2015; Macêdo et al., 2012). However, the action of ALA on EEG changes present in schizophrenia has not yet been determined. Since ALA is a potential adjunct drug in the treatment of schizophrenia this needs to be clarified.

The pharmacological model of schizophrenia induced by KET promotes changes in hippocampal EEG presenting thus a translational value (Kocsis et al., 2013). The hippocampus, a part of the limbic system, is located in the temporal lobe and plays a crucial role in mental functions related to behavior and memory (Zhang et al., 2016). Regarding memory, the hippocampus is involved in the storage and recall of memories and the formation of associations, functions that are disrupted in schizophrenia (Siekmeier and vanMaanen, 2014). These hippocampal functions are important in the pathophysiology in schizophrenia.

Therefore, the present study investigated the effects of CP alone or combined with ALA in the hippocampal average spectral power changes using the pharmacological model of schizophrenia induced by KET.

2. Methods

2.1. Animals

The experiments were performed in male Wistar rats (200–300 g). The animals were kept at a room with controlled temperature (23 ± 1 °C) with a cycle of 12 h light/dark and free access to food and water. All experimental procedures were performed in accordance with Guide for the Care and Use of Laboratory Animals from the National Research Council. The protocols were approved by the Ethics Committee of Federal University of Ceará (No. 92/2009).

2.2. Drugs

Alpha-lipoic acid (ALA - Sigma-Aldrich, St. Louis, EUA - ALA 100 mg/kg) dissolved in 5% carboxymethyl cellulose (CMC), ketamine hydrochloride (König, Brasil - KET 10 mg/kg) and chlorpromazine (Cristália, Itapira, Brazil – CP 1 or 5 mg/kg) were used. The controls received saline 0.9%. All solutions were administered in a volume of 0.1 ml for each 100 g of body weight.

2.3. Outline of the study

2.3.1. Electroencephalographic study

2.3.1.1. Stereotactic surgery and electrodes implantation. The rats were first anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). During the surgical procedure bipolar and twisted electrodes of NiCr wire (diameter 150 μm) were implanted in the hippocampus through stereotactic device (Stoelting®, EUA) at the following coordinates (mm): AP = −4.0, ML = ±2.6, and DV = −3.5 from bregma, according to the Atlas of Paxinos and Watson (1998). An additional screw was placed in the frontal bone cavity as the reference electrode. The electrodes were fixed to the skull with dental acrylic cement. The correct location of the implanted electrodes in the hippocampus was verified by histological analysis using violet cresyl staining according to Magni et al. (2007, 2011).

2.3.2. Treatment protocol

Three days after the electrodes implantation (Magni et al., 2007), the animals were randomly divided into nine groups (n = 6 animals/group). The treatment groups received 10 days administration of the drugs (each one administered once a day) being divided as follows: group 1 – control - 0.9% saline intraperitoneal (IP) injection; group 2 - KET 10 mg/kg, IP; group 3 – ALA 100 mg/kg, per os; group 4 - CP 1 mg/kg, IP; group 5 – CP5 mg/kg, IP; group 6 - CP1 + KET10 with a 30 min interval between drugs; group 7 - CP5 + KET10 with a 30 min interval between drugs; group 8 - ALA 100 mg/kg, per os + CP1 + KET10 with a 30 min interval between drugs; group 9 - ALA100 + CP5 + KET10 with a 30 min interval between drugs (Fig. 1).

The EEG recordings were taken from the hippocampus of animals *in vivo* on the 1st, 5th and 10th days of treatment, immediately after the last drug administration (Fig. 1).

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