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Ketamine ameliorates depressive-like behaviors and immune alterations in adult rats following maternal deprivation

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HIGHLIGHTS

- Maternal deprivation induced depressive-like behavior in adulthood rats.
- Maternal deprivation enhanced cytokines in periphery of adulthood rats.
- Ketamine reversed behavioral and immune alteration induced by maternal deprivation.

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ABSTRACT

A growing body of evidence points toward an association between the glutamatergic system, as well as immune system dysregulation and major depression. So, the present study was aimed at evaluating the behavioral and molecular effects of the ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor of glutamate in maternally deprived adult rats. In deprived rats treated with saline, we observed an increase in the immobility time; however, ketamine treatment reversed this effect, decreasing immobility time. In addition, maternal deprivation induced an increase in cytokines: TNF-α and IL-1in serum, and in IL-6 in serum and cerebrospinal fluid (CSF). Interestingly, ketamine treatment reduced the levels of all the cytokines in deprived rats. In conclusion, these findings further support a relationship between immune activation and depression. Considering the action of ketamine, this study suggested that antagonists of the NMDA receptor, such as ketamine, could exert their effects by modulation of the immune system.

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1. Introduction

Major depression is a psychiatric disorder that affects millions of people around the world, and despite existing treatments, many patients do not respond to them [1,2]. Thus, numerous studies have been conducted with the aim of better understanding the neurobiology of this disorder, as well as finding pharmacological targets with faster actions and more effectiveness [3–7]. The glutamatergic system is one such target of study in depression. This theory is supported by the fact that patients with depression exhibit elevated levels of glutamate in serum and brain tissue [8,9], and mainly because antagonists of N-methyl-D-aspartate (NMDA), such as ketamine, have been presenting antidepressant effects in animal models, as well as rapid onset in humans with depression [10–14].

Abnormalities in the glutamatergic system could lead to alterations in other pathways. For example, an overactivation of NMDA

Abbreviations: CSF, cerebrospinal fluid; IL-1, interleukin-1; IL-6, interleukin-6; NMDA, N-methyl-D-aspartate; TNF-α, tumor necrosis factor alpha.

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receptors due to elevated levels of glutamate, leads to a massive entry of calcium into cells. This causes an imbalance in calcium levels resulting in impairment of mitochondrial function and increased production of free radicals and oxidative stress, beyond increased inflammatory processes [15–17]. In fact, increased levels of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, IL-12, interferon (IFN)-γ and tumor necrosis factor-α (TNF-α) have already been related in patients with depression [18–20]. On the other hand, antidepressants reduce pro-inflammatory cytokine profiles and inflammatory markers in patients with depression [21,22].

As depression is a disorder with unknown causes and many patients are treatment-resistant, animal models are presented as important tools for investigating the etiology, as well as progress in the development of effective therapeutic targets for depression. It is known that early adverse life experiences represent one of the major risk factors for the development of mental disorders such as major depression. The early postnatal period is characterized by considerable plasticity of the developing nervous system. As such, the early postnatal environment is critical in its capacity to influence adult behavior [3,23].

Although some of the mechanisms of action of conventional antidepressants have been established, it is not yet entirely clear how ketamine exerts such effects. So, the present study was aimed at evaluating the effects of ketamine on behavior and cytokine levels in the serum and cerebrospinal fluid (CSF) of adult rats submitted to maternal deprivation. This is an important animal model because in rodents, this model mimics early life neglect/loss of parents in humans, and has been presented as one of the most potent natural stressors during development [24]. Moreover, maternal deprivation is an animal model that presents all criteria to the validity, for example, rodents subjected to maternal deprivation presents anhedonic behavior (face validity), neuroendocrine changes (construct validity), and classic antidepressants are able to reverse these alterations (predictive validity) [24].

2. Materials and methods

2.1. Animals

For this study, pregnant female Wistar rats (age of 3 months, weight of 250–280 g) were obtained from the breeding colony of Unesc (Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil) and were housed for one week in the presence of males for sexual experience. At the end of 7 days, pregnant rats were housed individually with ad libitum access to food and water. All mothers and pups were kept on a 12 h light/dark cycle (06:00 a.m. to 06:00 p.m.) at a temperature of 23 ± 1 °C. Male and female pups were used during the maternal deprivation period. On the first day after birth, the litters were culled to eight pups (four males and four females). The day of the sexual experience was marked as day zero. One day after the births occurred, the maternal deprivation protocol was applied to 50% of the male pups from days 1–10 after birth; other males were used as controls. After this, the animals were weaned at 21 days of age and housed with five animals per cage. Females were donated to the Unesc vivarium for other studies. Only male rats were used in this research and were divided into two experimental groups: (1) control (non-deprived), which received no treatment whatsoever; (2) deprived, which were submitted to maternal deprivation as described. All experimental procedures involving animals were performed in accordance with the NIH Guide for the Care and Usage of Laboratory Animals, also within the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care, and also with approval by the local Ethics Committee under protocol number 89/2011.

2.2. Maternal deprivation protocol

The pups were deprived of the mother for 3 h per day during the first 10 days. The maternal deprivation protocol consists of removing the mother from the nest box, and keeping the pups in the box to stand in the presence of maternal odor. Non-deprived animals remain undisturbed in home cage with their mother. We prefer this maternal deprivation protocol because it does not require manipulation of the pups [25].

2.3. Drugs and treatment

Ketamine was obtained from For Dodge (Brazil). When the animals reached 3 months of age, they received a dose of ketamine 15 mg/kg, intraperitoneally, once a day for 14 days. The doses of ketamine and treatment times are in agreement with previous studies [10,11,26,27]. The treatments were administrated at a volume of 1 mL/kg. For this study, in adulthood, the animals were divided into four groups with 10–12 animals per group: (1) non-deprived + saline; (2) non-deprived + ketamine; (3) deprived + saline; (4) deprived + ketamine. The drugs were administered 1 h before the forced swimming test.

2.4. Forced swimming test

The forced swimming test was conducted according to previous reports [10,11,26–29]. On day 13 of chronic treatment with ketamine, 1 h after drug administration, the rats were individually placed in the cylinder containing water for 15 min (pre-test session). On the 14th day the rats received the last intraperitoneal drug treatment, and after 1 h the rats were subjected to the forced swimming test for a 5-min session (test session) to evaluate the immobility time. Immediately after the forced swimming test, under anesthesia, blood and cerebrospinal fluid (CSF) were collected for subsequent analyses of cytokine levels ($n = 5–6$). The peripheral blood was collected by cardiac puncture, and CSF was drawn, by direct puncture of the cisterna magna with an insulin syringe (27 gauge 31/20 length). Individual samples of CSF that presented visible blood contamination were discarded.

2.5. Cytokine analysis

The concentrations of cytokines (IL-1β, IL-10 and TNF-α) were determined in serum and CSF ($n = 5–6$) by ELISA (R & D Systems, Minneapolis, MN) by dilution in an extracting solution containing PBS.

2.6. Statistical analysis

All data are presented as mean ± S.E.M. Differences among experimental groups in the forced swimming test and in the assessment of cytokine levels were determined by two-way ANOVA, followed by Tukey post hoc test when ANOVA was significant; P values < 0.05 were considered to be statistical significant.

3. Results

The effects of the administration of ketamine on the immobility times are illustrated in Fig. 1. The analysis by two-way ANOVA revealed significant differences for ketamine treatment ($F_{(1–65)} = 7.222$; $p = 0.009$; Fig. 1) and for deprivation vs. ketamine treatment interaction ($F_{(1–65)} = 6.893$; $p = 0.010$; Fig. 1) on the immobility times. Post hoc analysis indicated that deprivation significantly increased the immobility time, when compared to non-deprived rats. Ketamine treatment reversed the increase in the immobility time of deprived rats.

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