

Research report

Acute administration of ketamine reverses the inhibition of mitochondrial respiratory chain induced by chronic mild stress

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ABSTRACT

Modulation and dysfunction of the glutamatergic system seems to be involved in depression. Recently a renewed interest in the glutamatergic system as a treatment option for major depression emerged by the finding that the glutamate *N*-methyl-D-aspartate (NMDA) antagonist ketamine leads to a rapid improvement of depressive symptoms. Several works support the hypothesis that metabolism impairment is involved in the pathophysiology of depression. We have also recently reported that mitochondrial respiratory chain complexes I, III and IV were inhibited in cerebral cortex and cerebellum of rats after 40 days of chronic mild stress (CMS), which is used as an animal model of depression. Thus, we investigated whether the inhibition of these enzymes may be reversed by acute administration of ketamine (15 mg/kg). We verified that CMS decreased the intake of sweet food and ketamine was not able to reverse such effect. Adrenal gland weight was increased in stressed rats and ketamine reversed this alteration. Control group gained weight after 40 days but stressed group did not gain weight after the same period. Stressed animals gained weight after acute administration of ketamine, when compared to the body weight assessed at the beginning of the experiment. Finally, we verified that complexes I, III and IV were inhibited after CMS in cerebral cortex and cerebellum and acute administration of ketamine reversed this inhibition. Based on the present findings, we hypothesized that CMS induces inhibition of mitochondrial respiratory chain (complexes I, III and IV) and that acute administration of ketamine reverses such effect.

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1. Introduction

The treatment of depression was revolutionized about a half century ago by the discovery of monoamine oxidase inhibitors and tricyclic antidepressants. Since then, the availability of newer drugs with better adverse effects profiles has greatly increased our ability to safely treat a significant percentage of patients [45]. It is widely accepted that at least 20% of all depressed patients do not respond adequately to several antidepressant drugs. The exact mechanism for these effects is still unknown [24].

The challenges for the design of new agents to treat depression are threefold: rapid onset of antidepressant response, broader efficacy, and fewer adverse effects. While progress has been made to reduce side effects, currently available antidepressants do not show convincing evidence for a shorter delay of onset of therapeutic actions neither for improved efficacy on the treatment of major depression [11,12,20,25]. Thus, there is clearly a need to develop rapidly acting and potent treatments for major depression.

Modulation and dysfunction of the glutamatergic system seems to be involved in depression. Glutamate is the primary excitatory neurotransmitter in the mammalian brain. Glutamatergic neurotransmission may be modulated in the brain by different receptor types, including ionotropic and metabotropic receptors. In this context, studies have pointed to the ionotropic glutamate *N*-methyl-D-aspartate (NMDA) receptor as an important player in the etiology of psychopathologies, such as anxiety and major depression [23,17,22,40].

Unlike monoaminergic antidepressants, ketamine acts directly at the NMDA receptor and thereby may bypass long neurotrophic signaling cascades, which in turn could be the reason for the delayed effects of traditional antidepressants [24]. Recently a renewed interest in the glutamatergic system as a treatment option for major depression emerged by the finding that the NMDA antagonist ketamine leads to a rapid improvement of depressive symptoms [29].

Besides the glutamatergic system, several recent works also support the hypothesis that metabolism impairment is involved in the pathophysiology of depression [42,18,28,32,39]. Mitochondrial oxidative phosphorylation is the major adenosine triphosphate (ATP) producing pathway, which supplies more than 95% of the

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total energy requirement in the cells [4]. Mitochondrial dysfunction results from alterations in biochemical cascade and the damage to the mitochondrial electron transport chain has been suggested to be an important factor in the pathogenesis of a range of neuropsychiatric disorders, such as bipolar disorder, depression and schizophrenia [33]. In this context, we have recently reported that mitochondrial respiratory chain complexes I, III and IV were inhibited in cerebral cortex and cerebellum of rats after 40 days of chronic mild stress (CMS); CMS is a model of depression which consists of exposing animals sequentially to a variety of mild and unpredictable stressors (e.g. isolation, water and food deprivation, restraint, forced swimming, flashing light exposure) for several days [33,34,9]. We have also demonstrated that complex II and creatine kinase were not affected [34].

Considering that we have recently demonstrated that mitochondrial respiratory chain complexes I, III and IV were inhibited in cerebral cortex and cerebellum of rats after 40 days of CMS and that ketamine leads to a rapid improvement of depressive symptoms, we investigated whether the inhibition of these enzymes may be reversed by this drug.

2. Materials and methods

2.1. Animals

Male Wistar rats (300 g) were obtained from Central Animal House of Universidade do Extremo Sul Catarinense. The animals had free access to food (rat chow) and water, except for the stressed group during the period when the stressor applied required no food or water. The rats were maintained on a 12-h light-dark cycle (lights on 7:00 am), at a temperature of $23 \pm 1^\circ\text{C}$. The experiments were carried out in accordance with the National Institutes of Health Guide for the Use and Care of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior (SBNeC) recommendations for animal care, with the approval of UNESCO Ethics Committee. Moreover, all efforts were made to minimize animal suffering as well as to reduce the number of animals.

2.2. Chronic mild stress (CMS) model

CMS protocol was adapted from the procedure described by Rezin et al. [34] and Gamaro et al. [9]. The animals were divided in control and stressed groups. Controls were kept undisturbed in their home cages during the 40 days of treatment; a 40-day variate-stressors paradigm was used for the animals in the stressed group. Stress application started at different times everyday, in order to minimize its predictability.

2.3. Drugs and treatment

After 40 days of CMS, the animals were divided in four groups, as follows: (1) control + saline, (2) control + ketamine, (3) CMS + saline, and (4) CMS + ketamine. Ketamine (Fort Dodge Animal Health, Fort Dodge, IA, USA) at the dose of 15 mg/kg (as previously reported by Garcia and colleagues to evoke antidepressant-like effects) was injected intraperitoneally, one day after CMS procedure [11,12]. After that, the anhedonia test was performed.

2.4. Consumption of sweet food

After 40 days of CMS, consumption of sweet food was measured to verify anhedonia. The animals were placed in a lightened rectangular box (40 cm \times 15 cm \times 20 cm) with a glass ceiling, floor and side walls made of wood. This test was realized between 8:00 a.m. and 12:00 a.m. Ten Froot Loops (Kellogg's[®], pellets of wheat and corn starch and sucrose) were placed in each one extremity of the box. Animals were submitted to five trial sessions of 3 min, one per day, in order to become familiarized with this

food [7]. After being habituated, the animals were exposed to two test sessions, of 3 min each, after the five sessions of trained, when the number of ingested pellets was measured. When the animal ate part of the Froot Loops[™] (e.g. 1/3 or 1/4), this fraction was also considered. These two evaluations were made with the animals submitted to fasting (during a period of 22 h prior to the behavioral task) or with animals fed ad libitum. These evaluations were made since food deprivation, which is used in many behavior tasks as a motivating stimulus, may also be an acute stressor [19].

2.5. Adrenal gland and body weight

Body weight was measured at the beginning and at the end of the experiment. After killing the animals, the adrenal gland weight was evaluated as an indirect parameter of hypothalamic-pituitary-adrenal axis activation. Adrenal gland weight is usually increased in chronic stress, because glucocorticoids hormones are released by the adrenals in response to physical and psychological stressors.

2.6. Tissue and homogenate preparation

The animals were killed by decapitation, the brain was removed and cerebellum and cerebral cortex were homogenized (1:10, w/v) in SETH buffer, pH 7.4 (250 mM sucrose, 2 Mm EDTA, 10 mM Trizma base, 50 IU/ml heparin). The homogenates were centrifuged at $800 \times g$ for 10 min and the supernatants kept at -70°C until used for enzymes activity determination. The maximal period between homogenate preparation and enzyme analysis was always less than 5 days. Protein content was determined by the method described by Lowry et al. [26] using bovine serum albumin as standard.

2.7. Activities of mitochondrial respiratory chain enzymes

NADH dehydrogenase (complex I) was evaluated by the method described by Cassina and Radi [5] by the rate of NADH-dependent ferricyanide reduction at 420 nm. The activity of succinate: Cytochrome *c* oxidoreductase (complexes II–III) were determined according to the method of Fischer et al. [8], measured by Cytochrome *c* reduction from succinate. The activity of Cytochrome *c* oxidase (complex IV) was assayed according to the method described by Rustin et al. [35], measured by following the decrease in absorbance due to the oxidation of previously reduced Cytochrome *c* at 550 nm. The activities of the mitochondrial respiratory chain complexes were expressed as nmol/min mg protein.

2.8. Statistical analysis

Data were analyzed by one-way analysis of variance followed by the Tukey test when *F* was significant, and are expressed as mean \pm standard deviation (S.D.). All analyses were performed using the Statistical Package for the Social Science (SPSS) software.

3. Results

3.1. Consumption of sweet food

As showed in Table 1, CMS decreased the intake of sweet food, when compared to the control group. Acute administration of ketamine did not alter sweet food intake in control rats. Moreover, acute administration of ketamine was not able to reverse sweet food intake in rats submitted to CMS.

3.2. Adrenal gland and body weight

Adrenal gland weight was significantly increased in stressed rats when compared to non-stressed rats. Moreover, acute administration of ketamine reestablished a normal range of adrenal gland weight in stressed rats (Table 1). Body weights before and after 40

Table 1

Adrenal gland weight and mean intake of sweet food after CMS and body weight before and after CMS.

Group	Adrenal gland weight (mg)	Sugar pellets consumed	Body weight before CMS (g)	Body weight after CMS (g)
Control + saline	31.1 \pm 4.5	3.70 \pm 1.88	332.70 \pm 30.92	390.10 \pm 35.94*
Control + ketamine	32.8 \pm 3.3	4.06 \pm 0.96	335.73 \pm 35.41	376.13 \pm 37.56*
CMS + saline	45.3 \pm 4.2*	1.13 \pm 0.26*	345.64 \pm 16.98	365.71 \pm 29.98
CMS + ketamine	33.0 \pm 3.6	2.08 \pm 0.99*	343.14 \pm 28.04	374.57 \pm 24.55*

Data are expressed as mean \pm S.D. (*n* = 10). Different from control + saline.

* *p* < 0.05 (one-way ANOVA followed by Tukey).

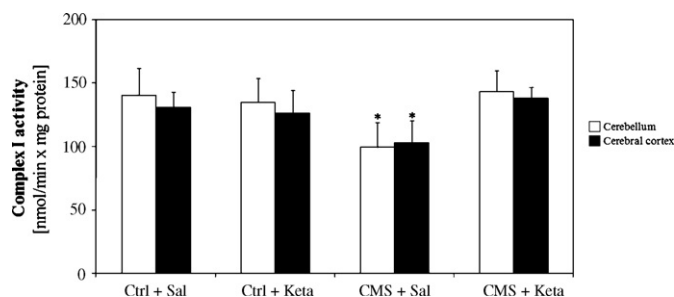


Fig. 1. Complex I activity in brain of rats subjected to CMS and treated with ketamine. Values are expressed as mean \pm S.D. ($n=10$). Different from control + saline; * $p < 0.05$ (one-way ANOVA followed by Tukey).

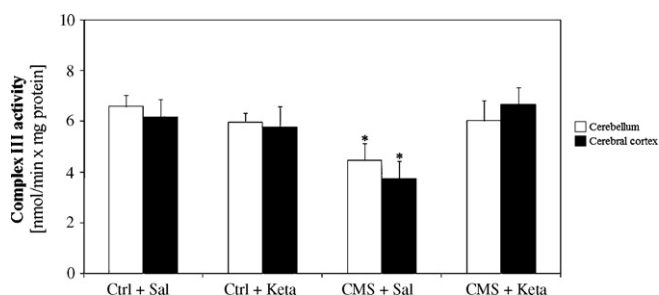


Fig. 2. Complex III activity in brain of rats subjected to CMS and treated with ketamine. Values are expressed as mean \pm S.D. ($n=10$). Different from control + saline; * $p < 0.05$ (one-way ANOVA followed by Tukey).

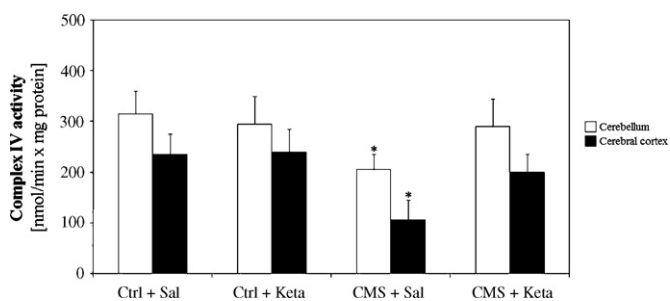


Fig. 3. Complex IV activity in brain of rats subjected to CMS and treated with ketamine. Values are expressed as mean \pm S.D. ($n=10$). Different from control + saline; * $p < 0.05$ (one-way ANOVA followed by Tukey).

days of CMS were also measured. The results showed that control group gained weight after 40 days but stressed group did not gain weight after the same period. Moreover, stressed animals gained weight after acute administration of ketamine, when compared to the body weight assessed at the beginning of the experiment (Table 1).

3.3. Activities of mitochondrial respiratory chain enzymes

As described previously [34], complexes I, III and IV were inhibited in stressed group in cerebral cortex and cerebellum. Moreover, acute administration of ketamine reversed the inhibition of complexes I, III and IV activities caused by CMS in these brain areas (Figs. 1–3, respectively).

4. Discussion

CMS used as an animal model of depression, was originally described by Willner et al. [43] and is characterized by chronic

unpredictable mild stressors. In the CMS model, both consumption and preference for sucrose intake is quite related to anhedonia [9,43,10,2]. In the present work, we observed that rats submitted to CMS decreased the intake of sweet food when compared to the control group. Acute administration of ketamine did not alter sweet food intake (in control group) and did not reverse decreased sweet food intake caused by CMS. In addition, stressed rats failed to gain body weight. However, after administration of ketamine, stressed animals gained weight when compared to the body weight assessed at the beginning of the experiment. CMS also induced an increase of rat adrenal gland weight, as previously described [21,15]. Moreover, the administration of ketamine reestablished a normal range of adrenal gland weight in stressed rats. Our present findings are in accordance to previous studies, which demonstrated that exposure to stress situations can influence feeding behavior and body weight of rats [9,2,6].

Additionally, several researchers hypothesized that metabolism impairment and dysfunction of the mitochondrial electron transport chain as important factors in the pathogenesis of a range of neuropsychiatric disorders, such as depression [34]. Gardner et al. [13] showed a significant decrease of mitochondrial ATP production rates and mitochondrial enzyme ratios in muscle in major depressive disorder patients. Madrigal et al. [27] also reported that complexes I–III and II–III of mitochondrial respiratory chain were inhibited in rat brain after chronic stress (immobilization for six hours during 21 days). We have also recently showed that activity of complexes I, III and IV was inhibited in cerebral cortex and cerebellum after 40 days of CMS [34]. In the present study, we showed that inhibition caused by CMS complexes I, III and IV was reversed by acute administration of ketamine.

Most cell energy is obtained through oxidative phosphorylation, a process requiring the action of various respiratory enzyme complexes located in a special structure of the inner mitochondrial membrane, the mitochondrial respiratory chain [37,16]. It is well known that mitochondrial oxidative phosphorylation system generates reactive oxygen species (ROS) and the electron transport chain, mainly complexes I and III, are vulnerable to damage by them [1,31]. Augmented ROS production causes defects in the mitochondrial genome, leading to impaired oxidative phosphorylation, which not only limits ATP generation but also further promotes ROS production [14,38]. In addition, the oxidative damage induced by CMS may be either the cause or the consequence of the mitochondrial dysfunction [4,27,41].

Berman et al. [3] showed that a single dose of ketamine produced antidepressant effects in patients suffering from major depression. Recently, Zarate et al. [45] extended this study to a higher number of patients, and they verified that the acute administration of ketamine rapidly improved depressive symptoms in patients with major depression. Therefore, these data strongly suggest that ketamine can induce robust and rapid antidepressant effects in depressed patients after a single intravenous injection.

It is also well demonstrated that oxidative stress (and excitotoxicity) may be either the cause or the consequence resulting from excessive activation of glutamate NMDA receptors [30,44]. Ketamine is a non-competitive antagonist of NMDA receptor for glutamate, which works in a use- and voltage-dependent manner. However, the effects of ketamine on oxidative stress parameters are still not clearly known. Some studies demonstrated that ketamine may present pro- [46] and antioxidant effects [36].

Taking together the present findings and evidence from the literature, we hypothesize that CMS induces inhibition of mitochondrial respiratory chain (complexes I, III and IV), probably by oxidative stress, and that acute administration of ketamine reverses such effect. We speculate that ketamine may exert the reversal effect by decreasing ROS production.

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