

Research Article

Alpha-Lipoic Acid Effects on Reserpine-Induced Depression-Like Behavior in Mice

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Keywords

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Abstract

The aim of this study was to investigate the effect of alpha-lipoic acid (ALA) in depression-like behavior in reserpine-induced changes in mice. Male Swiss mice (25-30g) received a single dose of saline solution (control), reserpine (RES 2 mg/kg), ALA (100 or 200 mg/kg), or a combination of ALA and RES. One hour after the last drug administration, the animals were submitted to behavioral tests of spontaneous locomotor activity test (SLA), rearing, grooming, rotarod, elevated plus maze (EPM), forced swimming test (FST) and tail suspension test (TST). The results showed no difference between treated animals and the control group in the SLA, grooming and rotarod test. However, reserpine presented an anxiogenic-like effect on the anxiety model studied. This effect was reversed by pre-treatment with ALA. In the meantime, reserpine induced a depression-like behavior in the FST and TST tests and these effects were also reversed by pre-treatment with ALA. The results suggest that the reserpine had an anxiogenic and depression-like effect, acting as a model for such behavior. Moreover, ALA reversed these effects suggesting its anxiolytic and antidepressant-like action.

ABBREVIATIONS

ALA: Alpha-Lipoic Acid; Res: Reserpine; SLA: Spontaneous Locomotor Activity; EPM: Elevated Plus Maze; FST: Forced Swimming Test; TST: Tail Suspension Test; MDD: Major Depressive Disorder; CNS: Central Nervous System; SOD: Superoxide Dismutase; CAT: Catalase; GSH: Glutathione Peroxidase; OFT: Open Field Test; NEOA: Number of Entries in the Open Arms; NECA: Number of Entries in the Closed Arms; TPOA: Time of Permanence in the Open Arms; TPCA: Times of Permanence in the Closed Arms

INTRODUCTION

Anxiety and depression, conditions that are often coexistent, are currently the most common and well-studied mood disorders in humans [1]. It was proposed that anxiety and depression may be a neuroendocrine continuum, in which anxiety occurs first during the lifetime of an individual and major depressive episodes occurs later on [2]. Major depressive disorder (MDD) is

a serious and often crippling psychiatric illness with a high risk of relapse and treatment resistance [3].

Several neurobiological hypotheses have been proposed to explain the pathophysiology of depression [4-6]. The theory of monoamines stands out for being one of the most accepted by the scientific community. Briefly, monoamine theories stipulate that depression is related to decreased levels of centrally available monoamines, noradrenaline or serotonin [7-9]. Based on this theory, drugs such as reserpine, that decrease concentrations of monoamines in the CNS, are used as pharmacological model for depressive-like behavior induced in rodents [10,11].

Studies show that reserpine can induce depression-like behavior in animals and drugs that prevent this action would, therefore, present an antidepressant effect [12-14]. Reserpine has been used in animal model to investigate the underlying mechanism of depression [15,16].

Clinical [17] and preclinical [18-20] studies have reported a number of oxidative disturbances in depression, including

elevated lipid peroxidation levels, decreasing activity of superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GSH) [21,22] and consequently may contribute to the dysfunction of serotonergic and noradrenergic systems [23]. In fact, alterations in oxidative stress may be an important trigger for stress induced atypical cardiomyopathy [24-26], and arrhythmias, conditioning a worse prognosis [27].

Thus it has been suggested that antioxidant substances could be an alternative treatment for CNS-related diseases, such as depressive disorders [20,28,29]. In recent years, our laboratory has been studying the action of the lipoic acid (ALA) in the CNS disorders [20,30-35]. ALA is an antioxidant naturally synthesized in human body. In its structural formula, there are 2 thiol groups that can be oxidized or reduced, therefore it is a redox couple [36]. Both the oxidized form and the reduced form (i.e., dihydrolipoic acid) of ALA act as antioxidants [36]. Dihydrolipoic acid is able to regenerate other antioxidants of low molecular weight, such as glutathione (GSH), coenzyme Q10, and vitamins A and C [37]. Moreover, ALA has demonstrated an anti-inflammatory activity and is thereby involved in the short-term and long-term reduction of oxidative processes related to neurodegenerative diseases [34,36]. In fact, as previously observed [26], ALA may be used as therapy to control and revert oxidative stress and sympathetic tone unbalance.

Although ALA has been studied in model of depression induced by corticosterone [20,30,33], no previous research has examined the role of ALA in preventing depression induced by reserpine. Therefore, the aim of this study was to investigate the ALA's ability to prevent anxiety and depression-like behaviors induced by reserpine in mice.

MATERIALS AND METHODS

Animals

Male Swiss mice (25-32 g) were obtained from the Animal House of the Federal University of Ceará, Brazil. In this study, one hundred twenty animals were kept in a room with a controlled temperature of 23°C, under a standard light-dark cycle with *ad libitum* access to food and water, except during the experiments. Food was removed 4 h prior to the oral gavage procedure and returned 60 min after. The animals were divided into one of the following five experimental groups (number 8-10 animals/group) according described in each respective legend. All experiments were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and all efforts were made to minimize the suffering of the animals and to reduce the number of animals used in the experiments.

Drugs

Reserpine (RES, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in a saline solution containing 0.1% dimethyl sulfoxide and 0.3% Tween-80. The dosage and route of administration for RES was selected based previous studies [12,38]. Alpha-lipoic acid (100 or 200 mg/kg - ALA, Sigma-Aldrich, St. Louis, MO, USA) was administered alone or 1 h before the administration of RES. The dosage and route of administration for ALA was selected based previous studies [20,26,29]. Control group received saline solution 0,9%. Desvenlafaxine succinate monohydrate

(DVS, Pristiq®, Wyeth Lab), used as a positive control in the forced swimming test (FST) and tail suspension test (TST), was dissolved in distilled water and administered by gavage (20 mg/kg) 1 hour before of reserpine.

Treatment protocol

The animals were randomly divided into experimental groups as shown in Figure (1).

Control group - Animals received saline solution (0, 9%), p.o. and, 1 hour after, another intraperitoneal injection with saline solution (0, 9%).

RES group - Animals received saline solution (0, 9%) p.o. and, 1 hour after, was administered reserpine 2 mg/kg by intraperitoneal injection.

ALA + Saline groups - Animals received ALA (100 or 200 mg/kg, p.o.) and, 1 hour after, was administered saline solution (0, 9%) by intraperitoneal injection.

ALA + RES groups - Animals received ALA (100 or 200 mg/kg, p.o.) and, 1 hour after, was administered reserpine 2 mg/kg by intraperitoneal injection.

DVS + RES group - Animals received (20 mg/kg, p.o.) and 1 hour after was administered reserpine 2 mg/kg by intraperitoneal injection.

Thirty minutes after the last administration the following behavioral tests were performed: Open field test (OFT), rota rod, elevated plus maze (EPM), forced swimming test (FST) and tail suspension test (TST).

Open field test

The open field test (OFT) area was made of acrylic (i.e., transparent walls and black floor, 30x30x15 cm) and divided into nine squares of equal area. The OFT was used to evaluate the exploratory activity of mice [39]. Each mice was placed in the center of the arena, and the number of squares crossed with all four paws (i.e., locomotor activity) over a 5 minutes period was recorded. The parameters observed included the following: number of squares crossed (i.e., locomotor activity), number of grooming events (i.e., body cleaning with paws, picking at the body and pubis with mouth, and face-washing actions), and number of rearing events (i.e., the animal standing on its hind legs or with its forearm against the wall of the observation cage or in the free air). Before introducing each animal to the area, the arena was cleaned with 5% alcohol to eliminate possible bias due to odors that could remain on the surfaces from the previous animals

Rotarod test

Animals were selected for the rota rod test before the pharmacological test. Mice were placed with the four paws on a 2.5 cm diameter bar, 25 cm above the floor and the time of permanence on the bar was measured for 1 min, for each animal. The rotating speed was of 12 rpm [40].

Elevated plus maze test

The EPM for mice consisted of two perpendicular open arms (30x5 cm) and two perpendicular closed arms (30x5x25 cm).

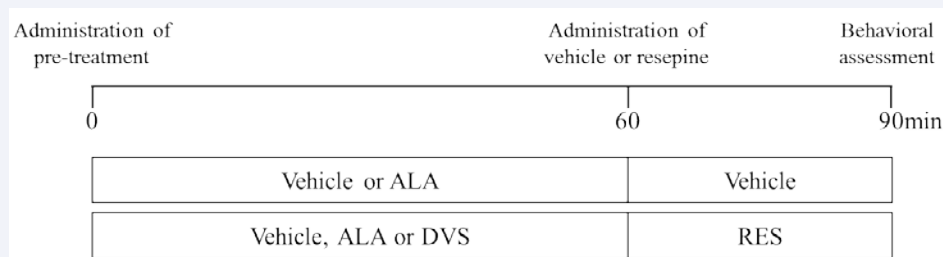


Figure 1 Schematic overview of experimental design.

Abbreviations: RES: Reserpine; ALA: Alpha-Lipoic Acid; DVS: Desvenlafaxine

The open and closed arms were connected by a central platform (5x5 cm). The platform and the lateral walls of the closed arms were made of transparent acrylic. The floor was made of black acrylic. The maze was 45 cm above the floor. After the respective treatment, each animal was placed at the center of the EPM with its nose in the direction of one of the closed arms and was observed for 5 min according to the following parameters: the number of entries in the open arms (NEOA); number of entries in the closed arms (NECA); time of permanence in the open arms (TPOA) and time of permanence in the closed arms (TPCA) [41].

Forced swimming test

Mice were individually forced to swim in an open cylindrical container (diameter, 22 cm; height, 40 cm) that contained 20 cm of water held at 25 ± 1 °C. The total time during which the mouse remained immobile during a 5 min period was recorded. Immobility was defined as the animal floating in the water without struggling and making only very minimal movements necessary to keep its head above the water. An increase in the duration of immobility is an indicative of depressive-like behavior [42].

Tail suspension test

For the tail suspension test (TST), each mouse was suspended by the tail on the edge of a shelf placed 58 cm above a table top. The mouse was secured in place via adhesive tape placed approximately 1 cm from the tip of the tail. The time during which the mouse remained immobile over a 6-min period was recorded [43].

Statistical analyses

Statistical analysis was performed with Graph Pad Prism 6.0 for Windows, Graph Pad Software (San Diego, CA, USA). The results were evaluated by one-way ANOVA followed by Turkey's test *post hoc*. All results are expressed as means \pm S.E.M (standard errors of the mean).

RESULTS AND DISCUSSION

Our data showed that administration reserpine (RES), alpha-lipoic acid (ALA) or group of pre-treatment with ALA (ALA+RES) did not alter the parameter number of crossings [$F(5, 45) = 2.180$; $p=0.0731$], and grooming [$F(5, 35) = 0.5938$; $p=0.7047$] in OFT. Groups treated with RES, ALA100+RES and ALA200 + RES showed a significantly decreased number of rearing [$F(5, 39) = 40.10$; $p<0.0001$] when compared to control group (Figure 2).

It was also observed that in the rotarod test none of the

treatments were able to cause changes in motor coordination of animals [$F(5, 54) = 0, 9011$; $p=0, 4872$] (Figure 3).

Results presenting in Figure (4) showed the data obtained from elevated plus maze test. In this test, reserpine decreased significantly the NEOA and TPOA [NEOA: $F(5, 44)=12.77$; $p<0.0001$; TPOA: $F(5,45)=12.69$; $p<0.0001$] and caused a significant increase in NECA and TPCA [NECA: $F(5,38)=10.81$; $p<0.0001$; TPCA: $F(5, 43)=28.95$; $p<0.0001$]. The pre-treatment with ALA was able to reverse the effects caused by reserpine in all parameters.

In forced swimming test (Figure 5) and tail suspension test (Figure 6), as expected, reserpine caused a significant increase in immobility time [FST: $F(6, 50)=26.18$; $p<0.0001$; TST: $F(6, 46)=17.87$; $p<0.0001$]. Pre-treatment with ALA100 or 200 reversed this effect, in both tests, showing a similar effect as presented by antidepressant desvenlafaxine, used as a positive control.

The spontaneous locomotor activity (SLA) test is used as a general parameter in investigating the central action of a drug. A decrease in locomotor activity means that the drug has a depressing effect on the CNS in the studied animal, i.e., there is a motor change that may interfere with other behavioral tests conducted in the same animal. Our results showed that reserpine did not interfere with SLA tests, suggesting that other tests performed would not be compromised by the animal's locomotor activity. However, the decrease of rearing was observed in animals treated with reserpine only and when associated with ALA. Rearing behavior, an exploratory act displayed by mice when placed in a novel situation, also has been used as an indicator of anxiety in the OFT [44,45].

A deficit in motor coordination would very likely affect performance in the forced swimming and tail suspension tests. In this way, we aimed to investigate the effects of reserpine and ALA in the rotarod test, a classical animal model used to evaluate peripheral neuromuscular blockage. Our findings showed that no treatment was able to change the motor coordination of the animals in this test. Thus, the effects observed in the immobility time is probably not related to peripheral neuromuscular blockage, but may involve neurons that control central depressant activity [46,47].

The present study showed that the administration of reserpine in mice was able to induce anxiety-like effects in the EPM, which were reversed by ALA. The EPM test is considered one of the most

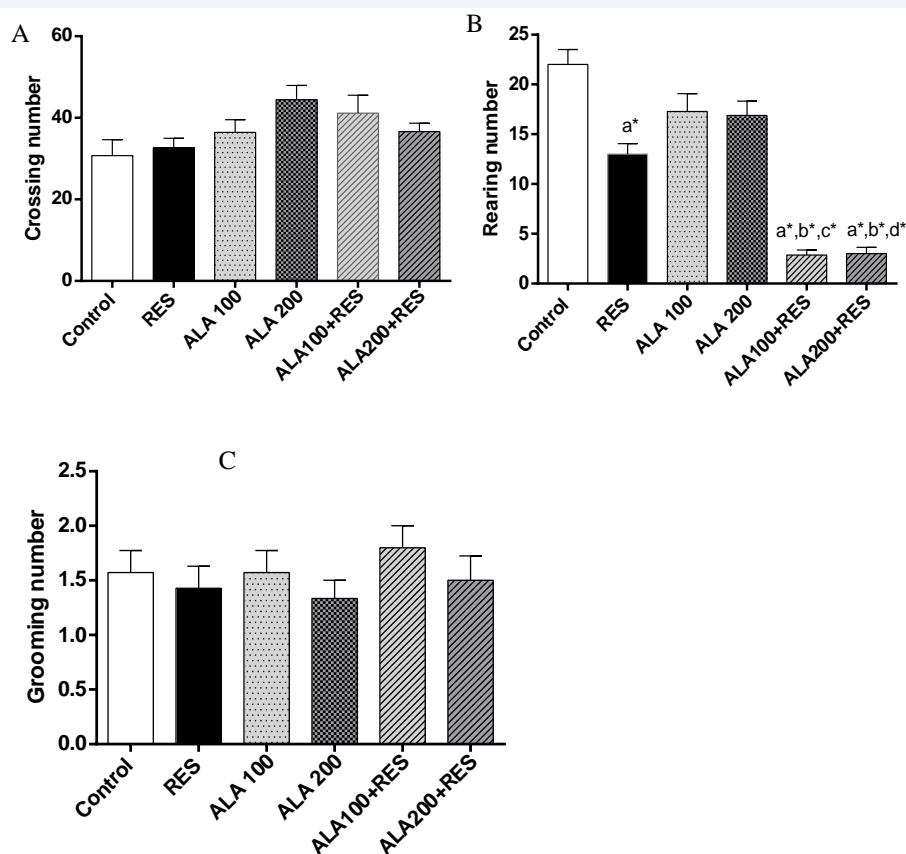


Figure 2 Effects of pretreatment with ALA in reserpine-induced depressive-like behavior in Number of crossings (A), rearings (B) and groomings (C) in open-field test. Each bar represents the mean \pm SEM of $n = 5-10$ animals/group. ^{a,b,c,d} $p < 0.05$ (*) vs. control, RES, ALA100 and ALA200 according to one-way ANOVA followed by Tukey's test *post hoc*.

Abbreviations: RES: Reserpine; ALA: Alpha-Lipoic Acid

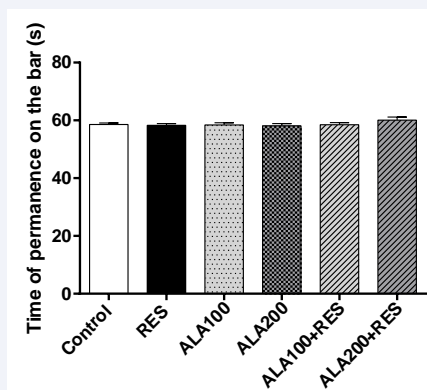


Figure 3 Effects of pretreatment with ALA in reserpine-induced depressive-like behavior in Rota rod test. Each bar represents the mean \pm SEM of $n = 10$ animals/group, according to one-way ANOVA followed by Tukey's test *post hoc*.

Abbreviations: RES: Reserpine; ALA: Alpha-Lipoic Acid

widely validated tests for assaying new anxiolytic agents [48,49]. In fact, several studies have shown that ALA has anxiolytic effect in depression models [32,33], which corroborates our results. Given that reserpine is a pharmacological model of depression based on its inhibitory effect on the vesicular monoamine

transporter 2, as well as showing a monoamines depleting action in the brain, we suggest that ALA possibly act by increasing monoamine neurotransmission.

FST and TST results showed, as expected, depressant effects of reserpine. Both tests remain as some of the most common animal models used for screening potential antidepressant agents [50]. These tests induce a state of immobility in animals facing an inescapable situation. Such immobility behavior has been hypothesized to reflect behavioral despair, which in turn may reflect depressive disorders in humans. Therefore, the antidepressant-like activity of a compound is expressed by a decrease in the immobility time of animals. This behavioral change is sensitive to major classes of antidepressant drugs, as desvenlafaxine. This drug is an active metabolite of venlafaxine, acting as a dual serotonin and noradrenaline reuptake inhibitor, and has shown superior clinical efficacy over other SNRI [51,52].

Our results showed that the pre-treatment with ALA reverted the depressant effects induced by reserpine in both models of FST and TST tests, in a similar manner as desvenlafaxine. This evidence suggests an excellent antidepressant effect of ALA. It is noteworthy that the antidepressant effect of lipoic acid has already been described by our group, mainly on models of depression induced by corticosterone [20,30,32,33].

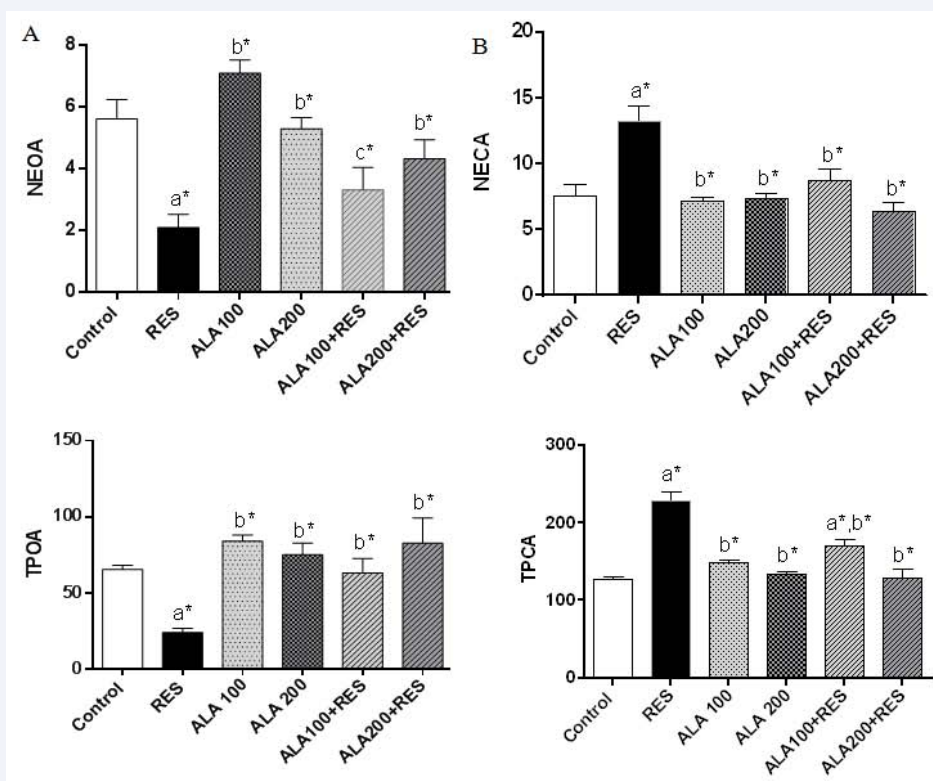


Figure 4 Effects of pretreatment with ALA in reserpine-induced depressive-like behavior in number of entries in open arms (A), number of entries in close arms (B), time of permanence in open arms (C) and time of permanence in close arms (D) in Elevated plus maze test. Each bar represents the mean \pm SEM of $n = 5-10$ animals/group. ^{a,b,c} $p < 0.05$ (*) vs. control, RES, ALA100, respectively, according to one-way ANOVA followed by Tukey's test *post hoc*.

Abbreviations: RES: Reserpine; ALA: Alpha-Lipoic Acid

CONCLUSION

Our results suggest that the reserpine present an anxiogenic and depression-like effect, acting as a model for such behavior. Moreover, ALA reversed these effects suggesting its anxiolytic and antidepressant-like action. In fact, ALA treatment may have important anti oxidative properties, and a modulative effect

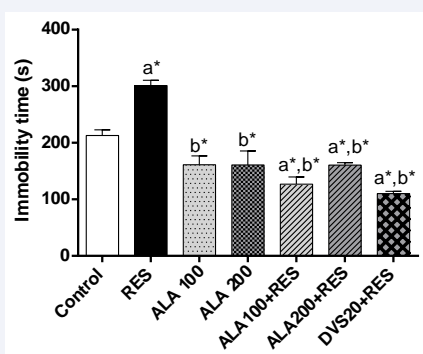


Figure 5 Effects of pretreatment with ALA in reserpine-induced depressive-like behavior in immobility time in Forced swimming test. Each bar represents the mean \pm SEM of $n = 7-10$ animals/group. ^{a,b} $p < 0.05$ (*) vs. control and RES, respectively, according to one-way ANOVA followed by Tukey's test *post hoc*. **Abbreviations:** RES: Reserpine; ALA: Alpha-Lipoic Acid; DVS: Desvenlafaxine

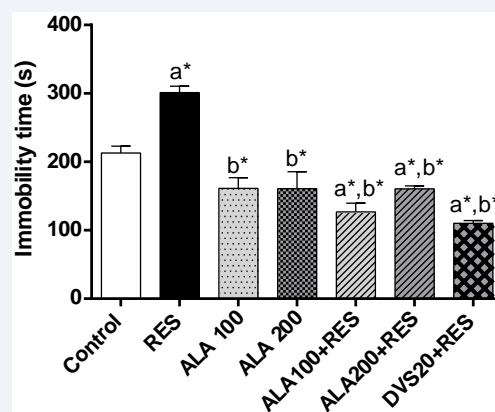


Figure 6 Effects of pretreatment with ALA in reserpine-induced depressive-like behavior in immobility time in Tail suspension test. Each bar represents the mean \pm SEM of $n = 8-10$ animals/group. ^{a,b,c} $p < 0.05$ (*) vs. control, RES, ALA100 and ALA200, respectively, according to one-way ANOVA followed by Tukey's test *post hoc*. **Abbreviations:** RES – reserpine, ALA alpha-lipoic acid, DVS - desvenlafaxine.

on sympathetic tone hyper activity [26,27]. This effect may be of great importance in numerous stress conditions, as on reserpine-induced depression-like behavior in a mice model. Lastly, these effects are most likely associated with ALA action on monoaminergic neurotransmission.

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