

## Acute Administration of Alpha-Lipoic Acid Does Not Affect Behavioural Despair in Mice Exposed to Tail Suspension Test

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### ABSTRACT

**Background:** Depression is a psychological condition associated with decrease in work performance, interpersonal relationship, financial status, and the appearance of suicide ideation. Possible causes of depression include: environmental influences, epigenetic and genetic factors. Decreased brain serotonin level has been implicated in the pathogenesis of depression. Alpha-lipoic acid (ALA) is a potent antioxidant synthesized via enzymatic reactions in the mitochondria. Alpha-lipoic acid possesses a wide array of metabolic benefits including increase in insulin sensitivity. Increased insulin sensitivity has been found to promote the formation of tryptophan leading to increased serotonin level. This study evaluated the effect of ALA on behavioural despair and non-spatial short-term memory in mice.

**Methodology:** Twenty-five (25) mice were grouped into 5 groups of five mice each. Group 1 received normal saline 10 ml/kg, Group 2 received imipramine 20 mg/kg, Groups 3, 4 and 5 were treated with graded doses of ALA 100, 200 and 400 mg/kg orally respectively for 3 days.

**Results:** The results revealed that acute administration of ALA did not significantly affect the immobility time (behavioural despair) in Tail Suspension Test (TST) when compared with normal saline and imipramine groups ( $p > 0.05$ ). In addition, there was no significant difference in percentage preference (short-term memory) between the ALA treated groups and the control group in Novel Object Recognition Test (NORT). In open field test, ALA 100 mg/kg group had significantly ( $p < 0.05$ ) increased locomotor activity (line-crossing) compared to normal saline and imipramine groups.

**Conclusion:** Acute administration of ALA for 3 days has no significant effect on immobility time and non-spatial short-term memory in mice.

**Keywords:** Alpha-lipoic acid, Depression, Antioxidant, Behavioural Despair, Memory

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## INTRODUCTION

Depression is a common mental disorder, characterized by persistent sadness and a loss of interest in activities that an individual normally enjoys, accompanied by an inability to carry out daily activities, for at least two weeks<sup>[1]</sup>. Brain regions that are involved in mood-regulating circuit such as hippocampus, temporal lobe, amygdala, caudate, anterior cingulate cortex, and frontal cortex have been found to be affected by depression<sup>[2]</sup>. Depression may result in premature death, major social and economic consequences. The core symptoms of depression include: depressed mood, diminished interest/pleasure and fatigue<sup>[3][4]</sup>. In addition to the well-defined depressive symptoms, patients suffering from MDD consistently complain about cognitive disturbances, significantly exacerbating the burden of this illness. Among cognitive symptoms, impairments in attention, working memory, learning and memory or executive functions are often reported<sup>[5]</sup>. The mechanism associated with depression is not yet fully understood and current treatments remain ineffective in large subset of patients<sup>[6]</sup>. However, in adult subjects with MDD, long-term therapy with certain antidepressants may be linked to cognitive side effects. For instance, treatment with antidepressants has been associated with increased cognitive deficits, such as apathy, inattentiveness, forgetfulness, word-finding difficulty, and mental slowing, in depressed individuals reaching partial or full remission<sup>[7]</sup>. Only about 35% of depressed patients achieve remission upon receiving treatment with antidepressants, despite many approaches available to treat depression and treatment response rates appear to reduce with each subsequent retry<sup>[8][9]</sup>. Alpha-lipoic acid (ALA), or 1,2-dithiolane-3-pentanoic acid, is a naturally occurring dithiol compound synthesized enzymatically in the

mitochondrion from octanoic acid. ALA is a necessary cofactor for mitochondrial  $\alpha$ -ketoacid dehydrogenases, and thus serves a critical role in mitochondrial energy metabolism. In addition to synthesis, ALA is also absorbed intact from dietary sources (such as potatoes, tomatoes and spinach), and it transiently accumulates in many tissues. Growing evidences have shown that orally supplied ALA may not be used as a metabolic cofactor but instead, elicits a unique set of biochemical activities with potential pharmacotherapeutic value against a host of pathophysiological insults<sup>[10]</sup>. Alpha-lipoic acid has become a common ingredient in multivitamin formulas, anti-aging supplements, and even pet food. It is well-defined as a therapy for preventing diabetic polyneuropathies, and scavenges free radicals, chelates metals, and restores intracellular glutathione levels which otherwise decline with age<sup>[10]</sup>. Due largely to its antioxidant properties, ALA has been reported to afford protection against oxidative injury in various disease processes, including neurodegenerative disorders such as depressive disorders<sup>[11][12]</sup>. Unlike most antioxidants, ALA is both water- and fat-soluble; thus, it can reach easily into tissues composed of fat, such as the nervous system as well as those mainly of water such as the cardiovascular system, so considered a “universal antioxidant”<sup>[13]</sup>. Furthermore, ALA can cross blood brain barrier<sup>[14]</sup>. This study is aimed at evaluating the effect of acute administration of ALA on behavioural despair and short-term memory in mice.

## MATERIALS AND METHODS

### Experimental Design and Animal Treatment

Twenty-five (25) apparently healthy Swiss Albino

mice of both sexes aged 6-8 weeks and weighing between 20-26 g were obtained from the Animal House of the Department of Human Physiology, Ahmadu Bello University, Zaria and allowed access to feed and water ad libitum. The mice were grouped into five groups (n=5). Daily administration was carried out orally based on daily body weight per mouse an hour before the commencement of the experiment for 3 days. Group I: received normal saline 10 ml/kg. Group II: were treated with Imipramine 20 mg/kg. Group III, IV and V: were treated with ALA at doses of 100 mg/kg, 200 mg/kg and 400 mg/kg respectively. Ethical clearance was obtained from Ahmadu Bello University Zaria Committee on Animal Use and Care with approval number: ABUCAUC/2017/003.

#### Drugs and Reagents

Alpha-lipoic acid was purchased from Novel Ingredient Services, West Caldwell, California, USA with a Product Code: A0030-301 and LOT # 671362552. Imipramine was purchased from Dr. Danladi Pharmaceuticals, Jos, Plateau State, Nigeria with NAFDAC Reg. No: A4-4872 and RES/11/03/C/13 manufactured by SYNMEDIC supplied by M.S.J. Industries Ltd Colombia.

#### Tail Suspension Test

The Tail Suspension Test (TST) was conducted according to the protocol adopted by Adem<sup>[15]</sup> and Can<sup>[16]</sup>. Each mouse was suspended by its tail with an adhesion tape of 17 cm on the model of the test which is a bar placed on a wood with dimension (55 height x 60 width x 12 cm depth). Each mouse was prevented from climbing its tail grasping the side walls by passing the tail through a plastic cylindrical tube. The immobility time (behavioural despair) which is the period where the mice are not moving

their body and paws was recorded using a stop watch in a period of 6 minutes for each animal. The walls of the apparatus were cleaned with 70% ethanol after each trial to prevent any olfactory cue.

#### Open Field Test (OFT)

The apparatus consists of floor space with dimension of 40 cm x 40 cm and 30 cm in height. The floor space was divided into 16 squares equally. Each mouse was given 5 minutes to explore the open field arena (test session). Line crossing (an index of locomotor activity) as indicated by the total number of squares crossed was measured during the test session<sup>[17][18]</sup>.

#### Novel Object Recognition Test (NORT)

Novel object recognition apparatus is a rectangular arena that was made of opaque plastic and measured 42 cm x 52 cm. The walls are 40 cm high. Mice were placed in the arena for 5-min where they encountered two identical sample objects (Sample Phase). At the end of the Sample Phase, mice were placed back in their home cages for a 5-min delay ( $\pm 15$  s). For the Testing Phase, animals were returned to the arena for 3-min where one of the familiar objects was replaced with a novel object. In addition to the arena, all objects were cleaned with 70% ethanol between each session. Successful novel object recognition was indexed by greater exploration of the novel compared to the familiar object. The discrimination ratio was calculated as the total time spent exploring the least recently seen object (novel object) divided by the time exploring both objects sampled at test (familiar objects), and percentage preference was calculated as the discrimination ratio multiplied by 100%<sup>[19]</sup>.

#### Statistical Analysis

The results were expressed as Mean  $\pm$  Standard Error of Mean (SEM). Comparisons between experimental and control groups were performed by one-way

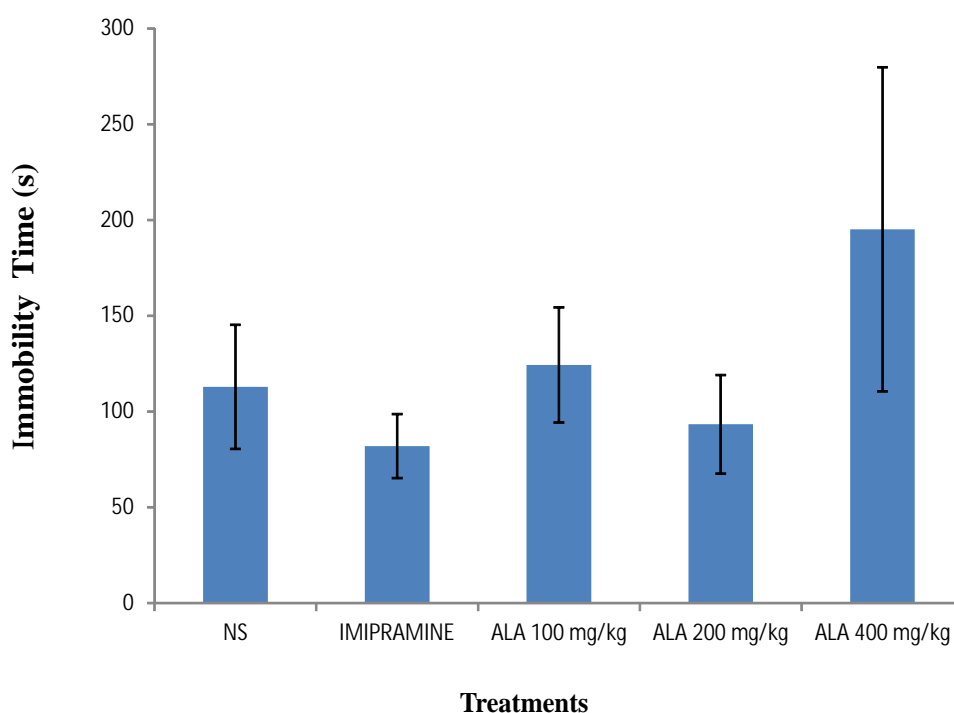
Analysis of Variance (ANOVA) followed by Tukey's HSD post hoc test for multiple comparisons with Statistical Package for Social Science (SPSS) version 22. Values with  $p < 0.05$  were considered statistically significant.

## RESULTS

Effect of Alpha-Lipoic Acid on Behavioural Despair in Mice using Tail Suspension Test.

The result of immobility time (behavioural despair)

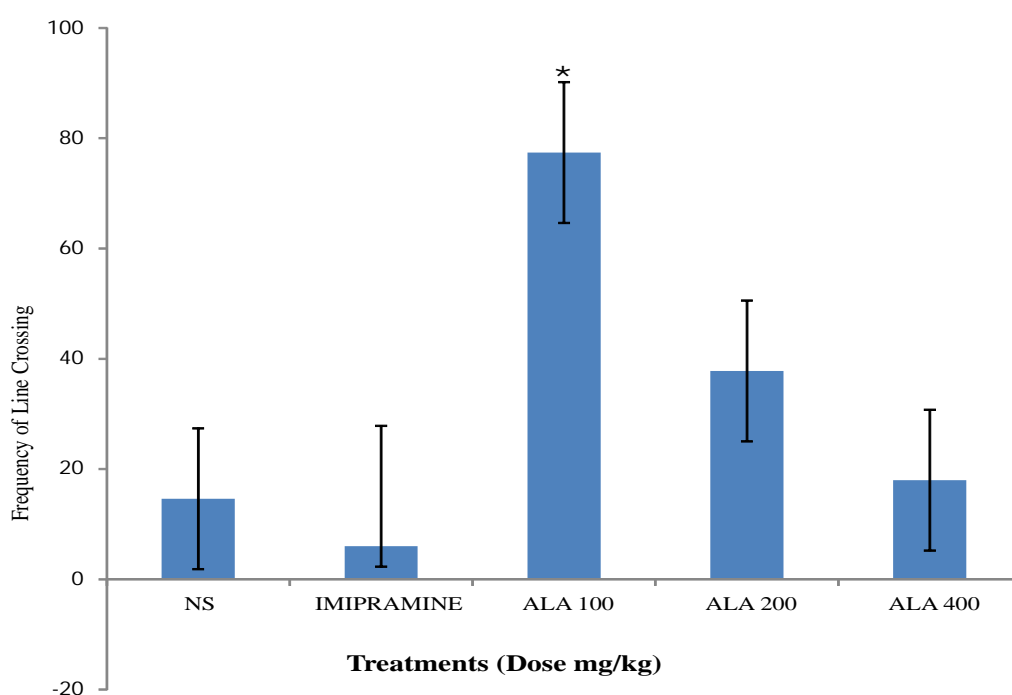
in tail suspension test showed no statistically significant ( $p > 0.05$ ) difference between the control and treated groups. The mean immobility time for the control group (normal saline 10 ml/kg), imipramine (20 mg/kg) and ALA (100 mg/kg, 200 mg/kg and 400 mg/kg) were  $113.00 \pm 32.40$ ,  $82.20 \pm 16.71$ ,  $124.40 \pm 30.11$ ,  $93.40 \pm 25.71$ , and  $195.20 \pm 37.81$  seconds respectively. Although not statistically significant, ALA 200 mg/kg showed decrease in immobility time compared to control group [ $F(4, 20) = 2.267$ ,  $p = 0.098$ ] (Figure 1).



**Figure 1:** Effect of Acute Administration of Alpha-Lipoic Acid on Behavioural Despair in Mice using Tail Suspension Test. Data was presented as mean  $\pm$  SEM,  $p > 0.05$  ( $n = 5$ ), SPSS version 22. ALA= Alpha-Lipoic Acid, NS= Normal Saline.

### Effect of Acute Administration of Alpha-Lipoic Acid on Locomotor Activity in Mice using Open Field Test.

In open field test, ALA 100mg/kg ( $77.40 \pm 11.00$ ) significantly increased frequency of line crossing (locomotor activity) when compared with the normal saline and imipramine groups ( $14.60 \pm 11.53$  and  $6.0 \pm 2.50$  respectively). Similarly, ALA 100mg/kg group had significantly higher mean line crossing than ALA 200 mg/kg and 400 mg/kg ( $37.80 \pm 11.25$ ,  $18.00 \pm 8.92$  respectively) with  $F(4, 20) = 8.739$ ,  $p = 0.000$  (Figure 2).



**Figure 2:** Effect of Acute Administration of Alpha-Lipoic Acid on Locomotor Activity in Mice using Open Field Test. \*= The mean difference was statistically significant when compared with control groups (normal saline and imipramine treated groups)  $p > 0.005$  ( $n=5$ ) SPSS version 22. NS= Normal Saline, ALA= Alpha-Lipoic Acid

### Effect of Alpha Lipoic Acid on Percentage Preferences (Non-Spatial Short-Term Memory) in Mice using Novel Object Recognition Test.

The result of Percentage preferences in novel object recognition test showed no statistically significant ( $p < 0.05$ ) difference between normal saline group ( $8.0 \pm 4.01$ ) and the treatment groups; Imipramine 20 mg/kg ( $19.04 \pm 8.96$ ) and ALA 100 mg/kg, 200 mg/kg, 400 mg/kg ( $14.16 \pm 4.74$ ,  $17.32 \pm 7.81$ , and  $18.08 \pm 7.38$ , respectively),  $F(4, 20) = 0.429$ ,  $p = 0.786$  (Table 1).

**Table 1:** Effect of Alpha-Lipoic Acid on Percentage Preferences (Non-spatial Short-Term Memory) in Mice Subjected to Novel Object Recognition Test

Group	Percentage Preference
Normal Saline 10 ml/kg	8.0 ± 4.01
Imipramine 20 mg/kg	19.04 ± 8.96
ALA 100 mg/kg	14.16 ± 4.74
ALA 200 mg/kg	17.32 ± 7.81
ALA 400 mg/kg	18.08 ± 7.38

Data expressed as mean ± SEM,  $p > 0.05$  ( $n = 5$ ),  
SPSS version 22. ALA=Alpha-Lipoic Acid.

## DISCUSSION

After acute administration of alpha lipoic acid in mice, the study found no significant difference in immobility time of tail suspension test of ALA versus the control groups. Although not statistically significant, the group treated with ALA 200 mg/kg showed decrease in immobility time (behavioural despair) when compared with the control groups, an indication of possible antidepressant-like effect. This might be due to antioxidant effect of ALA and its ability to be quickly absorbed by the body. Luc et al.<sup>[20]</sup> reported that ALA is quickly absorbed, then transported to the intracellular compartment where it is reduced to dihydrolipoic acid (DHLA) under the actions of lipoamide dehydrogenase enzyme. Furthermore, de Sousa et al.<sup>[21]</sup> reported that, ALA (200 mg/kg) showed an antidepressant-like effect by decreasing the preference of sucrose and reversing immobility time in the forced swimming test in female Swiss albino mice. In another study by de Sousa et al.<sup>[22]</sup>, ALA and desvenlafaxine (DVS), alone or combined, reversed corticosterone (CORT) effect on TST and striatum. This is an indication that ALA can be a promising agent for the treatment of depression and reversal of cognitive impairment by

reversing CORT-induced memory and social deficits. Similarly, Oliveira et al.<sup>[23]</sup> found that treatment with mirtazapine (MIRT) or MIRT+ALA for seven days was effective in reversing anxiety- and depressive-like behaviors induced by CORT possibly via their central antioxidant effects. However, Brian et al.<sup>[24]</sup> found that treatment with ALA at higher doses (600-1800 mg/kg) and acetyl-L-carnitine (ALCAR) for 12 weeks in humans did not have antidepressant effects in depressed bipolar patients and does not significantly enhance mitochondrial functioning in this patient group.

It is important to note some of our limitations in this study, especially the sample size which was small and might limit the statistical power. Similarly, we only focused on finding the effect of acute administration of ALA. Another possible reason for not observing significant effect in this our study might be due to the fact that ALA is a mitochondrial supplement. Berk et al.<sup>[25]</sup> suggested that mitochondrial supplements require a long period of time to yield beneficial effects.

Alpha-lipoic acid at dose 100 mg/kg was found to significantly increase line crossing (locomotor activity) in this study. This contradicts the findings of Saraswathy et al.<sup>[26]</sup> who reported that ALA did not have significant effect on locomotor activity in rats using actophotometer. However, we found ALA at doses of 200 and 400 mg/kg not significantly affecting locomotor activity. This is in agreement with the previous findings of Saraswathy et al.<sup>[26]</sup> in rats. This shows ALA is not a psychostimulant and might possess antidepressant-like activity, in accordance with report of Cryan et al.<sup>[27]</sup> who reported that psychotonics are clinically ineffective as antidepressants. They show anti-immobility effects in the TST but increase locomotor activity. In order to detect the possibility of a false positive result in anti-immobility effects, locomotor activity test

need to be conducted. The result for percentage preference (working memory) in this study revealed that ALA at all the doses did not significantly affect short term memory of the mice. This might probably be due to acute nature of this study. Although, Stoll et al.<sup>[28]</sup> found that ALA at dose of 100 mg/kg improved long-term memory of aged female Naval Medical Research Institute (NMRI) mice but could not significantly affect that of young mice subjected to habituation of open field test after administration of the ALA for 15 days. However, Saraswathy et al.<sup>[26]</sup> found that ALA (at doses 50, 100 and 200 mg/kg) reversed phenytoin-induced memory impairment of rats subjected to elevated plus maze test in a dose dependent fashion. Similarly, ALA reversed the cognitive deficit in high fat fed (HFF) rats in NORT<sup>[29]</sup>. The possible mechanism might be via prevention of alterations in insulin signaling thereby decreasing memory impairment by increasing vesicular glutamate transporter 1 (VGLut 1) which was found impaired in frontal regions of HFF Alzheimer's rats correlated with decline in cognition

## CONCLUSION

Acute administration of ALA for 3 days did not affect behavioural despair of mice exposed to TST. Nevertheless, there is need for further studies on efficacy of ALA in animal models of depression, and cognition.

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## Conflict of Interests

The authors declare that they have no conflict of interest.

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