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L-arginine as a potential antidepressant: Effects on cognitive function and antioxidant enzyme activity in depressed rats

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Abstract

The potential antidepressant effects of dietary *L*-arginine (*L*-Arg) were investigated in male white laboratory rats with corticosterone-induced depression. Daily administration of *L*-Arg at a dose of 150 mg/kg for 14 consecutive days significantly alleviated depressive-like behaviors and improved cognitive performance. Furthermore, *L*-Arg supplementation restored serotonin levels in the prefrontal cortex and hippocampus, which had been reduced following intraperitoneal corticosterone injection. To evaluate the antioxidant properties of *L*-Arg, quantitative changes in malondialdehyde (MDA) and nitric oxide (NO) levels were measured in the prefrontal cortex and hippocampal cells of depressive rats following *L*-Arg administration. The findings revealed that *L*-Arg normalized lipid peroxidation processes that had been enhanced under depressive conditions. *L*-Arg treatment significantly reduced elevated levels of these oxidative stress markers. Additionally, it increased the activity of key antioxidant enzymes, including mitochondrial superoxide dismutase (SOD) and catalase, whose activities had been suppressed in the depressive state. Kinetic analysis of enzymatic reactions indicated that the increased activity of these antioxidant enzymes in the brain cells of depressive rats was not due to structural modifications of the enzymes, but rather to an increase in their abundance. This effect is likely attributable to the activation of biosynthetic processes in brain cells triggered by *L*-Arg administration.

Keywords: Depression, *L*-arginine, fluoxetine, antioxidant system, corticosterone

Introduction

Depression is a prevalent mental disorder with serious personal and socio-economic consequences [1; 2]. It is characterized by a wide spectrum of symptoms that significantly impair quality of life [3]. Despite extensive research efforts, the precise pathophysiology of depression and effective treatment strategies remain incompletely understood. A growing body of evidence highlights the role of oxidative stress in the pathogenesis of depression, marked by increased production of reactive oxygen species (ROS) and diminished activity of antioxidant defense enzymes. Oxidative imbalance, in turn, disrupts essential metabolic processes. Antioxidants are known to protect mitochondrial structures and DNA from oxidative damage. During depression, mitochondrial dysfunction leads to ATP deficiency, impairing neuronal function and contributing to what is often referred to as "cellular energy depression" [4; 5]. Hormonal dysregulation, particularly involving the hypothalamic-pituitary-adrenal (HPA) axis, also plays a critical role in depression. Activation of this system can promote free radical production. For example, elevated cortisol levels observed in depressed patients may be caused by oxidative damage to receptor systems or reduced cytochrome P450 activity, both of which can be linked to oxidative stress [6; 7]. However, despite continued investigation, the primary initiating mechanism of depression remains elusive. Most currently available antidepressants target monoaminergic pathways in the brain, acting primarily as enzyme inhibitors that prevent neurotransmitter degradation or block their reuptake. Nevertheless, these drugs are often associated with limited efficacy, a delayed onset of therapeutic action (typically 2–3 weeks or more), and various adverse effects [8; 9]. These limitations have led to a search for novel antidepressants that act through alternative mechanisms. In the late 1990s, interest grew around agents such as ketamine, which

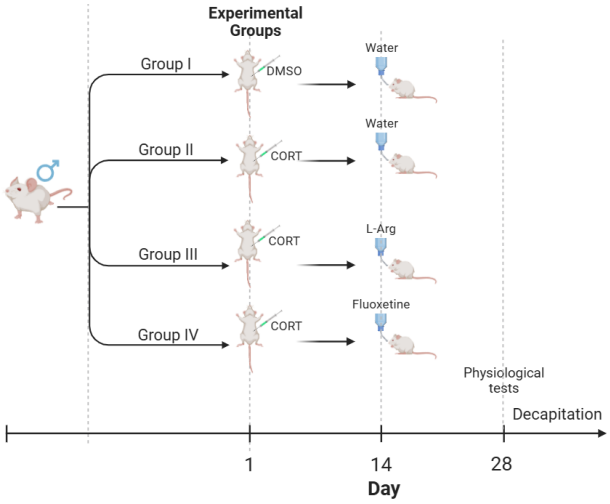

Figure 1. Scheme of studying the effect of exogenous L-arginine on depression induced by corticosterone administration.

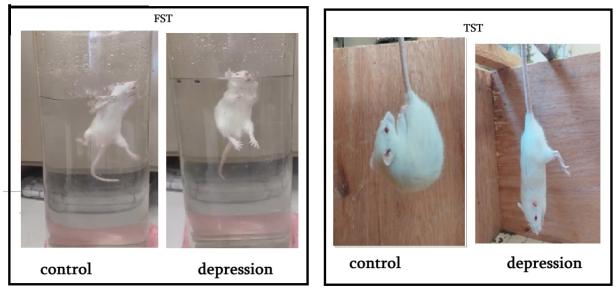

Figure 2. Study of corticosterone-induced depressive state in rats using the free swim test (FST) and tail-flick test (TST).

modulate the glutamatergic system [10; 11]. The rapid antidepressant action of ketamine has been attributed to activation of the mTOR signaling pathway in the hypothalamus and prefrontal cortex. However, the clinical utility of ketamine is limited by its side effect profile [12; 13]. Given this context, the identification of new compounds with antidepressant effects and fewer adverse outcomes is of significant interest. One such candidate is the amino acid *L*-arginine. Dietary *L*-arginine is absorbed in the small intestine and distributed throughout the body. It is metabolized along several pathways: converted into ornithine and urea, acts as a nitrogen donor, participates in transamination, and facilitates the elimination of protein catabolites. Ornithine, a metabolic product of *L*-arginine, serves as a precursor for the synthesis of collagen and polyamines [14; 15]. In parallel, nitric oxide (NO), synthesized from *L*-arginine, functions as a key signaling molecule involved in vasodilation, synaptic plasticity, learning and memory, and the modulation of neuronal activity during stress and anxiety [16; 17].

Importantly, *L*-arginine has also been reported to exhibit antioxidant properties [18; 19]. It downregulates oxidative stress, at least in part, by enhancing the antioxidant system through upregulation of related enzymes. For example: *L*-arginine has been shown to stimulate glutathione synthesis and activate the Nrf2 pathway, contributing to a robust antioxidant response [20]. Based on this background, the present study aimed to investigate the effects of exogenous *L*-arginine on depressive-like behaviors in a rat model, to evaluate its potential antidepressant activity, and to elucidate the molecular mechanisms underlying its action.

Materials and Methods

Ethics approval

The study protocol was approved by the Institutional Review Board of Ivane Javakhishvili Tbilisi State University. All procedures were conducted in accordance with the guidelines for the care and use of laboratory animals (N58/187). The experimental work was performed at the Department of Biology, Faculty of Exact and Natural Sciences, in close collaboration with the Chair of Biochemistry.

Animals and housing conditions

Adult male white laboratory rats (weighing 100 ± 15 g) were obtained from the animal facility of the A. Natishvili Institute of Morphology, Tbilisi State University (Tbilisi, Georgia). Prior to the experiment, the rats underwent a 7-day acclimatization period to the vivarium conditions. Animals were housed under standard laboratory conditions: a 12 h light/dark cycle, ambient temperature of 22 ± 1°C, and relative humidity of 47 ± 2%. Food and water were provided *ad libitum*. The animals were randomly assigned to four experimental groups (n = 15 per group; **Figure 1**):

- **Group I (G1)** received daily intraperitoneal injections of 100 μL 100% Dimethyl Sulfoxide (DMSO) (sc-358801, Santa Cruz Biotechnology, Inc., Europe) for 14 consecutive days and served as the vehicle control group.
- **Group II (G2)** received daily intraperitoneal injections of corticosterone (20 mg/kg) (sc-300391, Santa Cruz Biotechnology, Inc., Europe) for 14 consecutive days to induce depressive-like behavior.
- **Group III (G3)** received corticosterone as described for G2 during the first 14 days, followed by daily oral administration of L-arginine (150 mg/kg) (sc-391662, Santa Cruz Biotechnology, Inc., Europe) for an additional 14 days.
- **Group IV (G4)** received corticosterone as described for G2 during the first 14 days, followed by daily oral administration of fluoxetine (10 mg/kg) (sc-279166, Santa Cruz Biotechnology, Inc., Europe) for the next 14 days.

Behavioral assessments and biochemical analysis

To assess the emotional state and depression-like behavior of the experimental animals, the open-field test (OFT), forced

Table 1. Changes in some physiological parameters of experimental animals under the influence of dietary *L*-arginine under conditions of corticosterone-induced depression.

Behavioural parameters	I group	II group	III group	IV group
Crossed cells	255.5 ± 15.5	73.7 ± 18.7*	280.57 ± 20.8$^{\#\#}$	270.97 ± 22.4$^{\#\#\#}$
Number of positions in the centre	2.89 ± 0.5	0.4 ± 0.1**	2.757 ± 0.8$^{\#\#\#}$	2.607 ± 0.3$^{\#\#\#}$
Vertical posture	3.97 ± 0.7	0.5 ± 0.1***	6.97 ± 2.5$^{\#\#\#}$	5.557 ± 1.9$^{\#\#\#}$
Vertical posture with wall touching	13.5 ± 3.1	6.9 ± 1.1**	1.8 ± 0.3$^{\#\#\#}$	2.0 ± 0.4$^{\#\#\#}$
Duration of freezing (sec)	32.8 ± 3.8	127.7 ± 12.4***	40.3 ± 4.6$^{\#\#\#}$	38.8 ± 5.2$^{\#\#\#}$
Duration of grooming (sec)	18.9 ± 3.5	9.7 ± 2.9***	16.2 ± 3.1$^{\#\#}$	17.7 ± 2.4$^{\#\#\#}$
Defecation	2.5 ± 0.4	3.7 ± 0.9*	1.7 ± 0.1$^{\#}$	2.3 ± 0.1$^{\#}$
The duration of immobility in the FST (sec)	160.0 ± 15.1	210.6 ± 30.7**	100.5 ± 15.5$^{\#\#}$	140.9 ± 30.8$^{\#\#}$
The duration of immobility in the TST (sec)	50.5 ± 9.6	225.0 ± 25.9***	144.8 ± 35.8$^{\#\#}$	145.3 ± 47.4$^{\#\#\#}$

Data are shown as mean ± SD; *, the difference compared to control; $^{\#}$, the difference compared to CORT-induced depression; *,$^{\#}$, $p < 0.05$; **,$^{\#\#}$, $p < 0.01$; ***,$^{\#\#\#}$, $p < 0.001$

swim test (FST), and tail suspension test (TST) were performed **Figure** 2. These tests were conducted in accordance with the methodology described by [15]. In the FST, rats were placed in a cylinder filled with water for a total duration of 6 minutes, while in the TST, the animals were suspended by the tail for 5 minutes. A corticosterone solution (20 mg/mL) was freshly prepared each day in 100% dimethyl sulfoxide (DMSO) and administered intraperitoneally at a dose of 20 mg/kg, as outlined in **Figure 1**. The concentrations of nitric oxide (NO) and malondialdehyde (MDA), along with the enzymatic activities of superoxide dismutase (SOD) and catalase, were measured spectrophotometrically following previously described methods [16].

Statistical analysis

The obtained data were statistically analyzed using the SPSS software (version 23; SPSS Inc., Chicago, IL, USA). One-way ANOVA was employed in order to evaluate differences among the groups in physiological and biochemical parameters. When appropriate, either Tukeys HSD or Games-Howell post hoc tests were used to determine specific group differences. The results are presented as mean ± standard deviation (SD), and p-values less than 0.05 were considered statistically significant.

Results

Behavioral effects of *L*-arginine in a corticosterone-induced depression model

Corticosterone-induced depression significantly altered several important behavioral parameters in rats. Compared to the control group, the animals exposed to corticosterone exhibited clearly reduced exploratory activity, diminished cognitive function, and heightened anxiety-like behavior. Specifically, these animals demonstrated a marked and consistent decrease in the number of box crossings (by approximately 70%) and center entries (by about 80%). Conversely, the duration of freezing behaviora commonly used and widely accepted indicator of fearincreased by nearly 280%, thereby highlighting a substantial rise in anxiety levels **Table 1**. Furthermore, the forced swim test (FST) further supported the observed behavioral benefits of *L*-arginine, clearly showing a significant reduction in immobility time after treatment **Figure 1**. This particular outcome is consistent with an established antidepressant-like effect. A very similar trend was also observed in the tail suspension test (TST), where *L*-arginine administration significantly improved performance metrics compared to the untreated depressive group.

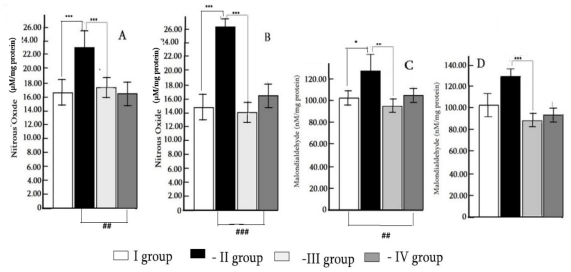

Figure 3. Effect of L-arginine on nitric oxide and malondialdehyde content in prefrontal cortex and hippocampal cells of depressed.

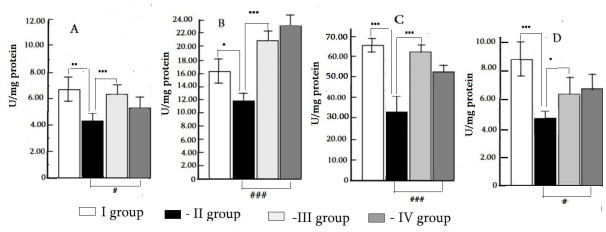

Figure 4. Effect of L-arginine on superoxide dismutase and catalase activity in prefrontal cortex and hippocampal cells of depressed individuals.

Effect of *L*-arginine on the hormonal status of depressed animals

Impact on serotonergic activity

Quantitative analysis of serotonin levels in the prefrontal cortex revealed a marked decline (approximately 28%) in corticosterone treated rats relative to controls **Figure 2**A. However, *L*-arginine supplementation led to a substantial increase (approximately 35%) in serotonin concentration compared to the untreated depressive group **Figure** 3A. Similar recovery patterns were observed in the hippocampus **Table** 2, indicating that *L*-arginine may exert its antidepressant effects at least in part via the restoration of monoaminergic neurotransmission. The results obtained also show that administration of the serotonin reuptake inhibitor fluoxetine produced similar effects in the depressed group of animals.

Effect of *L*-arginine on nitric oxide and malondialdehyde levels in the brain cells of depressed animals

Studies have shown a significant increase in nitric oxide levels in the prefrontal cortex and hippocampus of depressed individuals. However, 14-day administration of L-arginine to depressed animals significantly reduced these levels by approximately 30% and 35%, respectively **Figure 3 A and B**. Similar effects were observed with fluoxetine treatment.

Changes in malondialdehyde levels

Alterations were also observed in malondialdehyde (MDA) levels. As shown in **Figure 3 C and D**, corticosterone-induced depression is associated with an increased concentration of malondialdehyde in both the prefrontal cortex and hippocampal brain cells. However, *L*-arginine administration led to a reduction in its levels by approximately 20% in the prefrontal cortex and about 30% in the hippocampus. These findings suggest that corticosterone-induced depression is accompanied by increased lipid peroxidation, which decreases and approaches control levels following *L*-arginine treatment. As with previous parameters, fluoxetine administration similarly reduced malondialdehyde content.

Effect of *L*-arginine on the activity of antioxidant enzymes in depressed animals

The activities of key antioxidant enzymes superoxide dismutase (SOD) and catalasewere evaluated across the experimental groups, as presented in **Figure 4**. As shown in **Figure 4A**, SOD activity in the prefrontal cortex of depressed animals was significantly decreased (approximately 51%) compared to the control group. However, after 14 days of *L*-arginine administration, enzyme activity significantly increased and approached the control values. Similar trends were observed in the hippocampus **Figure 4 B**, although overall SOD activity in this region was lower than in the cortex across all groups.

Comparable patterns were noted for catalase activity. In the prefrontal cortex **Figure 4C**, catalase activity was reduced by approximately 47% in the depressed group, while *L*-arginine administration resulted in a 60% increase. Similar effects were also observed in the hippocampal cells **Figure 4D**. Importantly, fluoxetine treatment led to changes comparable to those observed with *L*-arginine. These results indicate that corticosterone-induced depression leads to decreased activity of antioxidant enzymes (SOD and catalase), while dietary *L*-arginine supplementation restores their activity.

Table 2. Quantitative changes in serotonin levels in the prefrontal cortex and hippocampus cells of depressed rats after receiving *L*-arginine.

Group	Prefrontal cortex	Hippocampus
I group	55.7 ± 9.8	58.9 ± 8.6
II group	38.3 ±6.3***	40.2 ±5.7**
III group	60.8 ±12.5$^{\#\#}$	50.0 ±5.5$^{\#}$
IV group	68.5 ±12.8$^{\#\#\#}$	52.7 ±7.4$^{\#\#}$

Data are shown as mean ± SD; *, the difference compared to control; $^{\#}$, the difference compared to CORT-induced depression; *,$^{\#}$, $p < 0.05$; **,$^{\#\#}$, $p < 0.01$; ***,$^{\#\#\#}$, $p < 0.001$.

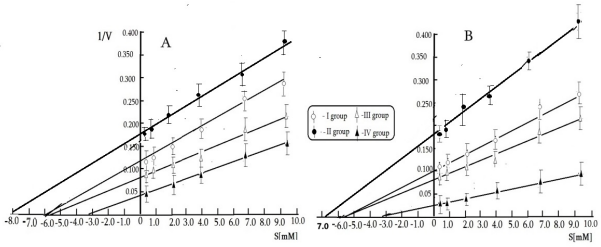

Figure 5. Effect of exogenous L-arginine on superoxide dismutase Vmax and Km in depressed rats.

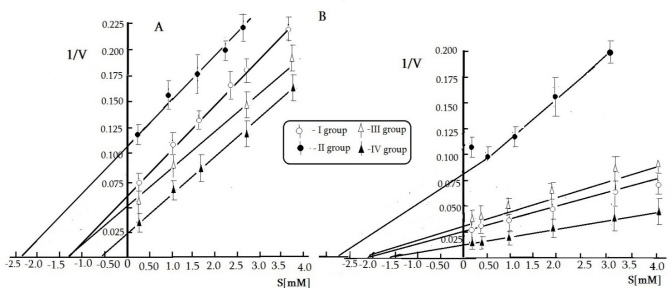

Figure 6. Effect of exogenous L-arginine on catalase V_{max} and K_m in depressed rats.

Notes: On the ordinate axis 1/V; on the abscissa axis substrate concentration (mM).

Kinetics of SOD and catalase and the effect of *L*-arginine

To investigate the mechanisms underlying enzyme activity changes, kinetic parameters were assessed. As shown in **Figure 5 A**, the maximum velocity (V_{max}) of SOD in the prefrontal cortex was decreased in the depressed group (Group II) compared to the control. However, V_{max} increased in Groups III and IV (arginine- and fluoxetine-treated groups, respectively). Interestingly, the Michaelis constant (K_m), indicating the enzyme's affinity for its substrate, remained nearly unchanged across all groups. Similar results were observed in the hippocampus **Figure 5 B**. (Note: On the ordinate axis 1/V; on the abscissa axis substrate concentration (mM)).

Similar results were obtained in the study of the kinetic parameters of the enzyme catalase. In particular, only the maximum velocity of the enzyme changed, while the affinity of the enzyme for the substrate (H_2O_2) remained the same **Figure 6**.

Discussion

This study aimed to investigate the effect of exogenous *L*-arginine on corticosterone-induced depression in albino rats. Our findings demonstrate that daily administration of *L*-arginine (150 mg/kg) for 14 days leads to improvements in behavioral and physiological parameters associated with depression. Notably, the open-field test results showed enhanced locomotor activity **Table 1** , while improvements in forced swim test (FST) and tail suspension test (TST) parameters further supported its antidepressant-like effects, in agreement with existing literature [21]. Serotonin, a key neurotransmitter, plays a critical role in the pathophysiology of depression, as evidenced by the efficacy of selective serotonin reuptake inhibitors (SSRIs) [8; 9; 22]. To clarify the mechanism underlying the observed effects, we measured serotonin levels in the prefrontal cortex and hippocampus. *L*-arginine supplementation significantly increased serotonin levels in both regions, closely resembling the effects of fluoxetine **Table 2**. This suggests that the antidepressant-like activity of *L*-arginine may be, at least in part, serotonin-mediated. Serotonin also exhibits strong antioxidant properties. A decrease in serotonin levels, as observed in depression, is associated with reduced antioxidant defense and elevated oxidative stress markers such as malondialdehyde (MDA) and nitric oxide (NO), along with decreased activity of antioxidant enzymes like glutathione peroxidase, superoxide dismutase (SOD), and catalase Hence, restoring serotonin levelseither pharmacologically (e.g., fluoxetine) or via *L*-arginine supplementationcan reduce oxidative stress in the brain [22; 23; 24].

In this study, we observed decreased MDA and NO levels following *L*-arginine administration **Figure 3**, suggesting a reduction in lipid peroxidation and nitrosative stress. These results support the notion that the antidepressant-like effect of *L*-arginine is mediated not only by serotonin enhancement but also by attenuation of oxidative stress [25]. Furthermore, we evaluated the impact of *L*-arginine on antioxidant enzyme activity. Corticosterone-induced depression significantly reduced SOD and catalase activities **Figure 4**, consistent with previous reports [26; 27]. *L*-arginine administration restored these activities, comparable to the effects observed with fluoxetine. To understand the mechanism behind these changes, we analyzed kinetic parameters (V_{max} and K_m) of SOD and catalase.

In corticosterone-treated rats, both V_{max} and substrate affinity (K_m) of the enzymes were reduced. However, *L*-arginine and fluoxetine treatments produced divergent outcomes. Fluoxetine increased both V_{max} and substrate affinity **Figure 5**, suggesting alterations in both enzyme expression and structure. These findings align with literature indicating that fluoxetines antioxidant effects may extend beyond serotonin modulation, potentially involving direct ROS scavenging [28; 29].

Conversely, *L*-arginine administration led to increased V_{max} without altering K_m, indicating an upregulation in enzyme quantity rather than structural modifications. These changes suggest that *L*-arginine stimulates enzyme synthesis **Figures 5, 6**, enhancing antioxidant capacity via increased enzyme availability rather than altered binding properties. Mitochondrial dysfunction and ATP depletion are well-documented in depression and contribute to impaired neuronal function and synaptic plasticity. *L*-arginine is a precursor for several metabolites, including creatine, which plays a crucial role in energy metabolism [30; 31]. Therefore, the observed effects of *L*-arginine may also be linked to its role in restoring cellular energy homeostasis, which is often compromised during depression.

Conclusion

Depression is a prevalent and debilitating psychiatric disorder with profound implications for individual well-being and societal productivity. The current study provides compelling evidence for the antidepressant-like effects of *L*-arginine in a corticosterone-induced model of depression. *L*-arginine supplementation significantly improved behavioral parameters and increased serotonin levels in key brain regions affected by depression. It also demonstrated potent antioxidant effects, as evidenced by reduced levels of oxidative stress markers (NO, MDA) and restored activities of crucial antioxidant enzymes (SOD and catalase). Kinetic analyses revealed that *L*-arginine enhances enzyme activity primarily by increasing enzyme synthesis, contrasting with the dual structural and quantitative effects observed with fluoxetine. Collectively, these findings suggest that *L*-arginine exerts its antidepressant-like effects through a dual mechanism involving both serotonin-mediated neurotransmission and improved antioxidant defense. Given its natural origin and multifaceted biological effects, *L*-arginine may serve as a promising adjunct or alternative to conventional antidepressant therapy. Further research is warranted to elucidate its precise molecular mechanisms and evaluate its clinical potential.

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