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# Antidepressant Effects of L-Arginine and Its Role in Brain Energy Metabolism

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**ABSTRACT**

**Background:** Mitochondrial dysfunction and impaired cellular energy metabolism are increasingly recognized as key contributing factors in depression. This study evaluated the amino acid L-arginine as a potential agent for behavioral rescue and bioenergetic restoration using a corticosterone-induced mouse model of depression.

**Methods:** Male mice were randomly assigned to four groups (n = 10): control (DMSO intraperitoneal [i.p.] + water oral gavage), corticosterone-induced depression (20 mg/kg, i.p. for 14 days), L-arginine treatment (150 mg/kg, oral gavage for 14 days), and fluoxetine (10 mg/kg, oral gavage for 14 days). To ensure handling equivalence, all oral administrations were performed via gavage (1.0 mL/100 g). Behavioral rescue was assessed via open field, forced swim (FST), and tail suspension (TST) tests. Hippocampal energy metabolism and PI3K/Akt/mTOR pathway activation were analyzed.

**Results:** L-arginine significantly improved the hippocampal bioenergetic profile, demonstrating efficacy comparable to the positive control fluoxetine. It led to a significant reduction in immobility time during FST and TST, alongside restoring glycolysis, the tricarboxylic acid cycle, and mitochondrial respiratory chain activities. Concurrently, L-arginine enhanced the activation state of the PI3K/Akt/mTOR signaling pathway (phosphorylated Akt/Akt and p-mTOR/mTOR ratios) and improved the functional state of the mitochondrial permeability transition pore. These metabolic and signaling improvements strongly correlated with the rescue of depressive-like behaviors.

**Conclusion:** Our findings demonstrate that L-arginine possesses potent antidepressant-like potential, mediated through bioenergetic restoration and signaling pathway modulation. By activating key metabolic processes in the hippocampus, L-arginine effectively restores impaired cellular energy homeostasis, suggesting its promise as a metabolic modulator for alleviating neurobiological disturbances associated with depressive conditions.
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*Keywords:* Arginine, Corticosterone, Depression, Energy metabolism, Hippocampus

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## 1. INTRODUCTION

According to recent data, the prevalence of psychiatric disorders has significantly increased worldwide, with depression ranking as the most common condition. This disorder is characterized by symptoms such as low mood, loss of motivation, sleep-wake disturbances, and suicidal ideation. The fact that depression poses a serious threat to human life highlights the urgent need for continued research into its mechanisms and treatment strategies[1-3].

Depression is a multifactorial disorder resulting from the combined effects of various biological and environmental factors, including neurotransmitter imbalances[4], chronic stress[5], and deficiency of neurotrophic factors[6]. Accumulating evidence suggests that impaired energy metabolism and mitochondrial dysfunction in brain cells represent critical mechanisms underlying depression[7-9]. For instance, reduced cerebral ATP levels are associated with a significantly higher risk of depression[10], while chronic stress can induce mitochondrial dysfunction in the prefrontal cortex and hippocampus, leading to diminished ATP levels and the onset of depressive-like behavior[11-14].

The connection between mitochondrial bioenergetics and depression is further supported by findings that certain compounds with antidepressant-like potential can enhance respiratory chain activity and increase ATP production[15,20]. Various agents, such as paroxetine, venlafaxine, and fluoxetine, have been shown to modulate mitochondrial complexes or aerobic glycolysis in regions like the hippocampus[16-19,21]. However, most currently used antidepressants are characterized by a relatively slow therapeutic onset and a range of undesirable side effects[22-24]. Moreover, treatment resistance in certain patients underscores the necessity of discovering less aggressive and more effective metabolic modulators for the treatment of depression. In this context, our study focuses on L-arginine as a potential candidate for bioenergetic restoration. L-arginine—an amino acid commonly used as a dietary supplement—is a precursor of nitric oxide (NO) and creatine, and exerts a strong influence on cellular energy metabolism[25]. While traditional monoaminergic antidepressants often fail to address mitochondrial failure, the role of L-arginine as a metabolic substrate makes it a strategic target for filling this therapeutic gap. NO signaling is complex, although the role of L-arginine in supporting mitochondrial function makes it a relevant target for addressing the metabolic deficits observed in depression.

Despite the known metabolic effects of L-arginine, its ability to rescue both behavioral deficits and hippocampal signaling impairments remains to be fully elucidated. Therefore, the aim of this study was to investigate the effect of oral L-arginine supplementation on depressive-like behaviors and the metabolic characteristics of total hippocampal homogenates in a model of depression induced by chronic corticosterone administration. By integrating behavioral assessments with biochemical analyses of the PI3K/Akt/mTOR pathway, we sought to determine if L-arginine-mediated bioenergetic restoration correlates with clinical-like behavioral recovery.

## 2. MATERIALS AND METHODS

### 2.1. Animals and housing conditions

Research activities were carried out at the Department of Biology (Ivane Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciences, Tbilisi, Georgia) in cooperation with the Chair of Biochemistry. Adult male white laboratory rats (body weight: 100 ± 15 g) were sourced from the A. Natishvili Institute of Morphology Animal Facility (TSU, Tbilisi). Animals were allowed a seven-day period to acclimate to the vivarium environment before the study. The housing conditions were strictly regulated: a 12-hour light/dark cycle, a constant temperature of 22 ± 1°C, and a relative humidity of 47 ± 5%. Standard laboratory chow and water were available ad libitum.

### 2.2. Experimental groups and treatment schedule

Rats were randomly allocated into four experimental groups (n = 10 per group): group I (G1) received daily intraperitoneal (i.p.) injections of 100 µL of pure dimethyl sulfoxide (DMSO; sc-358801, Santa Cruz Biotechnology, Europe) for 14 consecutive days. From day 15 to 28, animals had free access to untreated drinking water; group II (G2): administered corticosterone (20 mg/kg; sc-300391, Santa Cruz Biotechnology) once daily for 14 days to induce depressive-like behavior. From day 15 to 28, animals received untreated drinking water; group III (G3): treated with corticosterone (20 mg/kg/day) for 14 days, followed by L-arginine supplementation (150 mg/kg; sc-391662, Santa Cruz Biotechnology) for another 14 days, starting from day 15 to 28; group IV (G4): received corticosterone (20 mg/kg/day) for an initial 14 days, followed by fluoxetine (10 mg/kg; sc-279166, Santa Cruz Biotechnology) treatment for the subsequent 14 days (day 15 to 28). The focus on male rats was chosen to minimize the confounding influence of the estrous cycle on hormonal and behavioral stability, which is a common practice in initial behavioral screening. The hippocampus was selected as the primary region of interest due to its high density of glucocorticoid receptors and its well-documented vulnerability to corticosterone-induced neurotoxicity and structural remodeling. Throughout the 14-day corticosterone administration, no significant decrease in food or water consumption was observed across the groups. While G2 (CORT) showed a slightly slower weight gain compared to the control, there was no clinical weight loss or signs of "sickness behavior" (e.g., lethargy or ptosis). Furthermore, the open-field test (OFT) showed that while "exploratory" behavior decreased, the animals maintained basic motor coordination, ruling out non-specific metabolic suppression or physical impairment as the primary cause of the observed depressive-like state.





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### 2.3. Behavioral assessment and corticosterone preparation

To evaluate the emotional and depressive-like states in rats, the OFT, forced swim test (FST), and tail suspension test (TST) were employed. These assessments followed the methodology described previously[26].

### 2.4. Corticosterone administration

Corticosterone was prepared daily as a 20 mg/mL solution in 100% DMSO. To achieve the target dose of 20 mg/kg for rats weighing approximately 100 g, we administered a fixed i.p. injection volume of 100 µL per animal. This specific volume was chosen to minimize the systemic toxicity associated with DMSO. Although the median lethal dose ($LD_{50}$) of DMSO in rats is relatively high, we restricted the volume to 1 mL/kg (100 µL per 100 g body weight) to prioritize animal safety and prevent confounding solvent-related mortality or severe distress. The vehicle control group (G1) received an equivalent volume (100 µL) of pure DMSO to ensure consistency in handling and administration-related stress[27].

### 2.5. Revised vehicle and route administration

To ensure experimental consistency and minimize procedural bias, a double-vehicle approach was employed with strict handling equivalence across all groups. Corticosterone was dissolved in 100% DMSO and administered via i.p. injection at a volume of 0.1 mL per 100 g body weight. Correspondingly, the control group (group I) received an equivalent volume and frequency of pure DMSO (vehicle 1) via the same i.p. route. For oral treatments, L-arginine and fluoxetine were dissolved in distilled water (vehicle 2). To ensure precise dosing and maintain strict handling equivalence across all cohorts, all oral treatments—including distilled water for groups I and II—were administered daily via oral gavage. The procedures were performed at a fixed time (11:00–11:30 AM) using a standardized administration volume of 1.0 mL per 100 g of body weight. This procedure ensured the delivery of the calculated doses (L-arginine: 150 mg/kg; fluoxetine: 10 mg/kg) while guaranteeing that the procedural stress, handling frequency, and administration timing were identical for all experimental animals, strictly aligning with the experimental timeline (Fig. S1).

### 2.6. Sample preparation and protein quantification

Freshly collected hippocampal tissues were processed immediately to maintain enzymatic stability. Tissues were homogenized in ice-cold phosphate-buffered saline (pH 7.4) and centrifuged at 10,000 ×g at 4°C for 10 minutes. The resulting supernatant was collected and used for subsequent biochemical assays without delay. Total protein content was quantified using the Lowry method, with bovine serum albumin as the standard. This measurement was used to normalize all enzyme activity data across experimental groups (expressed as U/mg protein).

### 2.7. Chemicals and reagents

Unless otherwise specified, all chemicals and reagents used in the present study were purchased from Sigma–Aldrich (St. Louis, MO, USA).

### 2.8. Determination of glycolytic metabolism enzyme activity

To assess the functionality of glycolytic metabolism, we measured the activities of several key enzymes involved in glycolysis. The activity of hexokinase, which catalyzes the first step of glucose phosphorylation, was determined using a commercial assay kit (MyBioSource, San Diego, CA, USA; MBS9719202). The activity of aldolase, an essential enzyme that catalyzes the reversible cleavage of fructose 1,6-bisphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, was evaluated using the Fructose-Bisphosphate Aldolase Test Kit (MyBioSource, MBS265365). Pyruvate dehydrogenase (PDH) activity was determined using the Pyruvate Dehydrogenase Assay Kit (MyBioSource, MBS8243249). To further examine tricarboxylic acid (TCA) cycle activity, we analyzed the enzymatic function of several major enzymes, including aconitase (ACO; MBS8309682), α-ketoglutarate dehydrogenase (α-KGDH; MBS8309683), succinate dehydrogenase (MBS8243220), and fumarase (MBS7218132), each measured using their respective activity assay kits. In addition, creatine kinase, a crucial enzyme in cellular energy homeostasis, was investigated. The activity of the creatine kinase (CK) was quantified using the Abcam (Cambridge, UK) Creatine Kinase Activity Kit (Ab155901).

### 2.9. Determination of electron transport chain enzyme activity

Measurements of mitochondrial respiratory chain complex activity were used in the experiment. In particular, complex I activity (NADH: ubiquinone oxidoreductase) was evaluated using the MyBioSource kit (San Diego, CA, USA; MBS8806971), and the activity of complex II (succinate dehydrogenase) was measured by the MBS8243220 kit. Moreover, complex III (cytochrome $bc_1$ complex) was investigated using the complex III assay kit (MBS3805803), and the activity of complex IV (cytochrome c oxidase) was assessed by the MBS037447 kit. In addition, the activity of complex





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V (ATP synthase) was measured using the ATP synthase activity assay kit (MBS8305380).

### 2.10. Assay conditions and detection

All enzymatic reactions were performed at a controlled incubation temperature of 37°C. Incubation periods (typically 15–30 minutes) and detection wavelengths were strictly followed as per the specific requirements of each commercial kit to ensure optimal sensitivity and linearity of the results.

### 2.11. Determination of ATP levels

Intracellular ATP concentrations were quantified using the Luminescent ATP Detection Assay Kit (Abcam, Cambridge, UK; Ab113849) according to the manufacturer's protocol.

### 2.12. Assessment of mitochondrial permeability transition (MPTP) pore

MPTP was evaluated spectrophotometrically at 5[illegible] nm under room temperature conditions. The assay medium consisted of a mitochondrial suspension (approximately 0.5 mg/mL protein) prepared in a buffer containing 120 mM KCl, 3 mM $KH_2PO_4$, a[illegible] mM sodium succinate, all dissolved in 10 [illegible] Tris-HCl buffer (pH 7.4) supplemented with 250 [illegible] M sucrose. To induce pore opening, $CaCl_2$ (200 [illegible] was added to the incubation mixture, while cyclosporin A (0.42 µM) served as a specific inhibitor to block the pore. The extent of MPTP opening was determined by monitoring the corresponding changes in light absorbance[26].

### 2.13. PI3K/Akt/mTOR pathway analysis by Western blotting

For the evaluation of PI3K/Akt/mTOR signaling pathway activation, hippocampal protein samples were subjected to Western blot analysis following standard procedures[27]. Protein concentrations were determined using a BCA protein assay kit (Thermo Scientific, Waltham, MA, USA). The following primary antibodies were used: PI3 Kinase p85 (#4292), phospho-PI3K p85 (Tyr458, #4228), Phospho-Akt (Ser473) (#9271), Akt (#9272), Phospho-mTOR (Ser2448) (#2971), and mTOR (#2972) (all from Cell Signaling Technology, Danvers, MA, USA). β-actin was used as an internal loading control to ensure equal protein loading. Signal quantification from Western blots was performed using ImageJ software. To interpret pathway activation mechanistically, the phosphorylation state of each signaling molecule was expressed as the ratio of phosphorylated protein to its respective total protein (p/total). These ratios were then normalized and expressed as a percentage (%) relative to the control group to provide a comparative measure of pathway activation across experimental cohorts.

### 2.14. Statistical analysis

All statistical procedures were performed using SPSS software (version 23.0, IBM, Chicago, IL, USA). Group differences in physiological and biochemical parameters were assessed using one-way analysis of variance (ANOVA). For Western blot analysis, raw densitometric values were expressed as a ratio of phosphorylated protein to its respective total protein (p/total). When significant main effects were observed, Tukey's HSD post-hoc test was applied for multiple comparisons. Statistical significance was defined at $p < 0.05$.

## 3. RESULTS

### 3.1. Impact of L-arginine on psycho-emotional status in corticosterone-induced depression

The induction of depression in the animal model resulted in significant alterations in behavioral profiles. One-way ANOVA revealed significant differences across experimental groups for all assessed parameters, including locomotor activity ($F_{3,36} = 42.15$; $p < 0.001$), freezing duration ($F_{3,36} = 115.4$; $p < 0.001$), and immobility in the FST ($F_{3,36} = 38.6$; $p < 0.001$). As illustrated in Table 1, corticosterone-induced depression (group II) led to significant behavioral deviations compared to the control group (group I). Locomotor and exploratory activities were significantly impaired, with crossed cells decreasing (73.7 ± 5.71 in group II; 255.5 ± 4.9 in group I; $p < 0.05$) and center entries dropping (0.4 ± 0.03 in group II; 2.89 ± 0.15 in group I; $p < 0.01$). Conversely, anxiety-related behaviors were intensified; for instance, the duration of freezing in the depressed cohort increased significantly to 127.7 ± 3.92 s (group I: 32.8 ± 0.38 s; $p < 0.001$). The recovery of these parameters was evident in group III following 14 days of L-arginine treatment. Our data indicated that L-arginine administration effectively shifted behavioral markers back toward control levels ($p < 0.001$ compared to group II). Specifically, locomotor activity increased (280.57 ± 6.58 in group III), and freezing duration reduced (40.3 ± 1.46 s in group III). These outcomes were benchmarked against fluoxetine; notably, the therapeutic effects of L-arginine were comparable to those of fluoxetine (Table 1). The antidepressant-like efficacy of L-arginine was further validated by the FST results (Table 1), which showed that 14 days of treatment significantly improved performance indicators. Immobility time in the FST was reduced to 100.5 ± 4.90 s (group III) compared to 210.6 ± 9.71 s in group II ($p < 0.01$). Similar positive trends were recorded in the TST (Table 1), where L-arginine substantially enhanced the behavioral response, reducing immobility to 144.8 ± 11.33 s (group II: 225.0 ± 8.19 s; $p < 0.001$).





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**Table 1.** Effects of exogenous L-arginine on behavioral parameters in a corticosterone-induced rat model of depression

| No. | Behavioral parameters | Groups | | | |
|---|---|---|---|---|---|
| | | I | II | III | IV |
| 1 | Crossed cells | 255.5 ± 4.9 | 73.7 ± 5.71$^{*}$ | 280.57 ± 6.58$^{\#\#}$ | 270.97 ± 7.08$^{\#\#}$ |
| 2 | Number of positions in the center | 2.89 ± 0.15 | 0.4 ± 0.03$^{**}$ | 2.75 ± 0.25$^{\#\#\#}$ | 2.61 ± 0.09$^{\#\#\#}$ |
| 3 | Vertical posture | 3.97 ± 0.22 | 0.5 ± 0.03$^{***}$ | 6.97 ± 0.79$^{\#\#\#}$ | 5.56 + 0.60$^{\#\#\#}$ |
| 4 | Vertical posture with wall touching | 13.5 ± 0.98 | 6.9 ± 0.35$^{**}$ | 1.8 ± 0.09$^{\#\#\#}$ | 2.0 ± 0.12$^{\#\#\#}$ |
| 5 | Duration of freezing (s) | 32.8 ± 0.38 | 127.7 ± 3.92$^{***}$ | 40.3 ± 1.46$^{\#\#\#}$ | 38.8 ± 1.64$^{\#\#\#}$ |
| 6 | Duration of grooming (s) | 18.9 ± 3.50 | 9.7 ± 0.92$^{***}$ | 16.2 ± 0.98$^{\#\#}$ | 17.7 ± 0.76$^{\#\#\#}$ |
| 7 | Defection | 2.5 ± 0.34 | 3.7 ± 0.28$^{*}$ | 1.7 ± 0.03$^{\#}$ | 2.3 ± 0.03$^{\#}$ |
| 8 | Duration of immobility in the FST (s) | 160.0 ± 4.77 | 210.6 ± 9.71$^{**}$ | 100.5 ± 4.90$^{\#\#\#}$ | 140.9 ± 9.75$^{\#\#\#}$ |
| 9 | Duration of immobility in the TST | 50.5 ± 3.03 | 225.0 ± 8.19$^{***}$ | 144.8 ± 11.33$^{\#\#\#}$ | 145.3 ± 15.03$^{\#\#\#}$ |

Data are presented as mean ± SEM (n = 10 per group). Statistical significance was determined using one-way ANOVA followed by Tukey's HSD post-hoc test. Statistical significance: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus the control group (group I); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ versus the depressive group (group II).



### 3.2. Effect of L-Arginine on the enzymes of energy metabolism

To determine the impact of exogenous L-arginine on energy metabolism, we examined its effect on glycolytic enzymes in hippocampal tissue. One-way ANOVA revealed significant differences across all experimental groups for hexokinase (HK; $F_{3,36} = 6.31$; $p$ < 0.001), phosphofructokinase (PFK; $F_{3,36} = 135.8$; $p$ < 0.001), aldolase (ALD; $F_{3,36} = 8.74$; $p < 0.001$), glyceraldehyde 3-phosphate dehydrogenase (GAPDH; $F_{3,36} = 189.4$; $p$ < 0.001), and lactate dehydrogenase (LDH; $F_{3,36} = 36.45$; $p < 0.001$), as shown in Figure 1. Under depressive conditions (group II), HK activity was significantly increased compared to control levels ($p$ < 0.01), likely as a compensatory mechanism. In contrast, the activities of downstream enzymes, including PFK, ALD, GAPDH, and LDH, were markedly reduced, indicating a significant impairment of glycolytic flux. Administration of L-arginine to depressive animals (group III) successfully reversed these trends: it significantly increased the activities of PFK, ALD, GAPDH, and LDH ($p < 0.001$ vs. group II) while normalizing HK activity toward control levels ($p > 0.05$ vs. group I). These restorative effects were comparable to those observed in the fluoxetine-treated group (group IV; Fig. 1). The activity of PDH, which links glycolysis to the TCA cycle, was also significantly altered across groups ($F_{3,36} = 103.5$; $p < 0.001$). PDH activity was profoundly reduced in group II ($p < 0.001$ vs. control). However, in group III, L-arginine supplementation significantly increased PDH activity ($p < 0.001$ vs. group II), suggesting an improvement in the aerobic oxidation of glucose. Similar recovery was noted in group IV animals (Fig. 1).

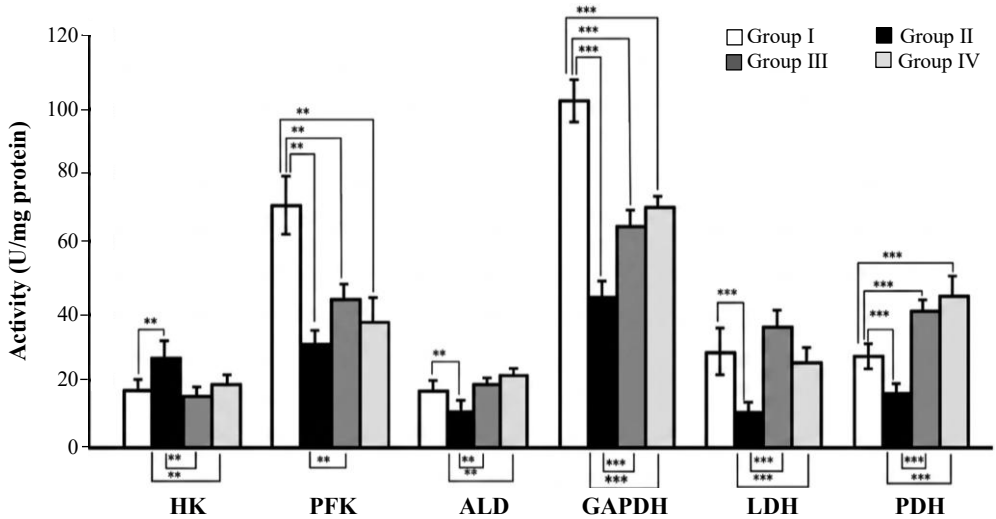


**Fig. 1.** Effect of L-arginine on the activities of HK, PFK, ALD, GAPDH, LDH, and PDH in the hippocampus of depressive rats. Data represent mean ± SEM (n =10 per group). Statistical significance was determined using one-way ANOVA followed by Tukey's HSD post-hoc test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for indicated comparisons between groups. Enzyme activity is expressed as U/mg protein.





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### 3.3. Effect of L-Arginine on the TCA cycle and mitochondrial respiratory complexes

Following the assessment of glycolytic processes, we examined the influence of exogenous L-arginine on the TCA cycle in hippocampal tissue (Fig. 2A). One-way ANOVA revealed significant differences across experimental groups for ACO ($F_{3,36} = 34.61$; $p < 0.001$), NAD-isocitrate dehydrogenase (NAD-IDH; $F_{3,36} = 101.5$; $p < 0.001$), α-KGDH ($F_{3,36} = 24.16$; $p < 0.001$), and fumarase ($F_{3,36} = 45.82$; $p < 0.001$). In depressive rats (group II), compared to controls, the activities of ACO, NAD-IDH, and α-KGDH were significantly decreased ($p < 0.05$ and $p < 0.001$, respectively). However, fumarase activity showed a non-significant change under depressive conditions ($p > 0.05$ vs. control). In group III animals, L-arginine administration markedly increased these activities, including a significant elevation in fumarase activity compared to both the control and depressive models ($p < 0.05$). NAD-IDH activity showed a particularly robust recovery, increasing by approximately 200% relative to group II ($p < 0.001$). Similar restorative effects were observed in the fluoxetine-treated group (group IV; Fig. 2A). Analysis of mitochondrial respiratory chain complex activities also revealed significant alterations across all groups (Fig. 2B): complex I ($F_{3,36} = 62.1$; $p <$ 0.001), complex II ($F_{3,36} = 138.4$; $p < 0.001$), complex III ($F_{3,36} = 38.14$; $p < 0.001$), complex IV ($F_{3,36} = 135$; $p < 0.001$), and complex V ($F_{3,36} = 18$; $p < 0.001$). Under depressive conditions (group II), the activities of complex I and complex III were reduced by approximately 40% ($p < 0.05$) and 60% ($p < 0.001$), respectively, compared to controls. In contrast, complex II and complex IV activities were significantly elevated in group II ($p < 0.01$ and $p < 0.001$, respectively). L-arginine treatment (group III) significantly modulated these activities toward control levels ($p < 0.05$ or $p < 0.01$ vs. group II; Fig. 2B). Complex V activity, which was markedly suppressed in group II ($p < 0.001$), also showed significant restoration following L-arginine supplementation ($p < 0.01$; Fig. 2B).

### 3.4. Effect of L-arginine on CK isoforms

To further clarify the role of L-arginine in energy metabolism, we evaluated its effect on the mitochondrial and cytosolic isoforms of CK (Fig. 3). Significant differences were observed across all experimental groups for both mitochondrial ($F_{3,36} = 135.2$; $p < 0.001$) and cytosolic ($F_{3,36} = 218.4$; $p < 0.001$) isoforms. In hippocampal homogenates from depressive rats (group II), CK activities were markedly reduced—by approximately 46% for the mitochondrial and 58% for the cytosolic isoform—compared to the control group ($p < 0.01$ and $p < 0.001$, respectively). Administration of L-arginine (group III) significantly restored these activities, resulting in a 64% increase in mitochondrial CK and a 110% increase in cytosolic CK activity relative to group II ($p < 0.001$). Comparable restorative effects were observed in the fluoxetine-treated group (group IV), where activities returned toward control levels (Fig. 3). These data align with the findings for ATP content in the hippocampal tissue (Fig. 4). In depressive rats, ATP levels were significantly depleted by 47% compared to controls ($F_{3,36} = 142.8$; $p < 0.001$). Dietary L-arginine administration (group III) markedly increased ATP concentration by 81% relative



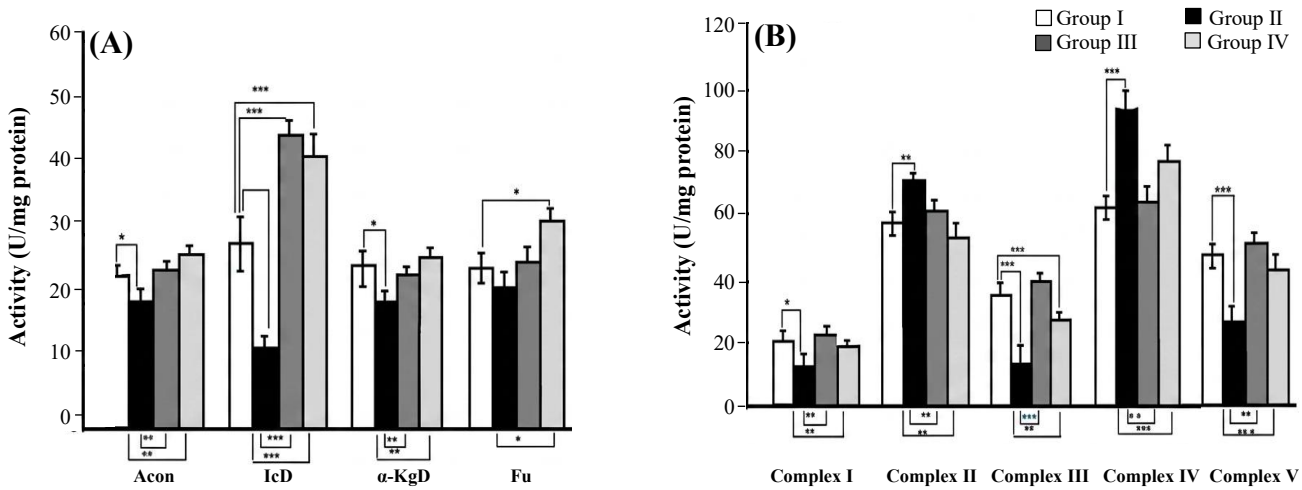


**Fig. 2.** Effect of L-arginine on mitochondrial bioenergetics in the hippocampus of depressive rats. (A) Activities of TCA cycle enzymes: ACO, NAD-IDH, α-KGDH, and fumarase. (B) Activities of mitochondrial respiratory chain complexes I-V. Data represent mean ± SEM (n =10 per group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for indicated comparisons. Enzyme activity is expressed as U/mg protein.



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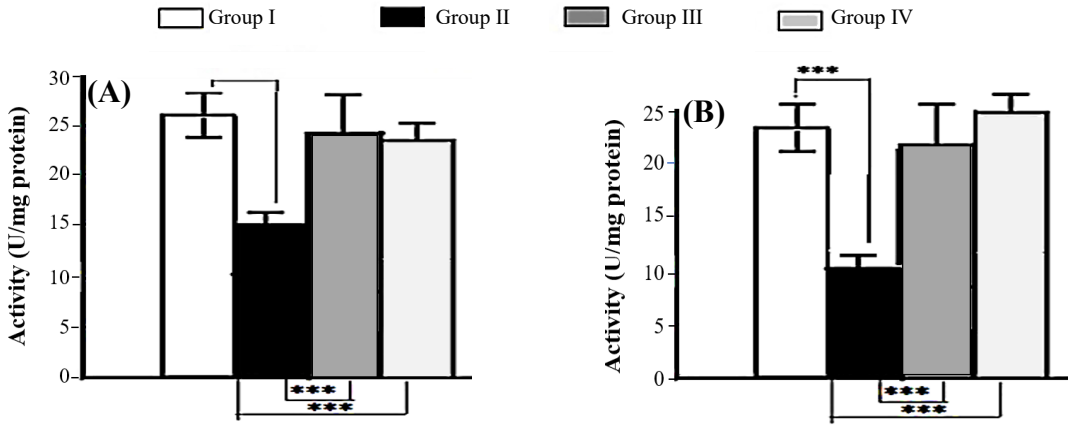


**Fig. 3.** Activity of mitochondrial (A) and cytosolic (B) isoforms of CK (U/mg protein). Data represent mean ± SEM (n=10 per group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

to the depressive model ($p < 0.001$), effectively restoring cellular energy stores. A similar recovery of ATP content (78% increase) was also documented in the fluoxetine-treated animals (group IV; $p < 0.001$; Fig. 4).

### 3.5. PI3K/Akt/mTOR signaling pathway

Given the L-arginine-induced changes in energy metabolism enzymes, we next investigated the involvement of the PI3K/Akt/mTOR signaling pathway (Fig. 5). One-way ANOVA revealed significant differences across groups for both native PI3K ($F_{3,36} = 129.6$; $p < 0.001$) and its phosphorylated isoform ($F_{3,36} = 71.9$; $p < 0.001$). In the depressive group (group II), compared to controls (group I), the level of native PI3K and its phosphorylated form were significantly reduced ($p < 0.001$). Administration of exogenous L-arginine (group III) markedly increased both native and phosphorylated PI3K levels ($p < 0.01$ vs. group II; Fig. 5B). While the total quantity of Akt protein showed less variation, significant alterations were observed in the levels of phosphorylated Akt (p-Akt) across the experimental groups ($F_{3,36} = 40.5$; $p < 0.001$). Specifically, p-Akt levels decreased in the depressive model but were significantly elevated following treatment in both the L-arginine and fluoxetine groups—by approximately 35% and 60%, respectively, compared to group II (Fig. 5B). Notably, the depressive state was accompanied by a significant reduction in both the native ($F_{3,36} = 72.0$; $p < 0.001$) and phosphorylated ($F_{3,36} = 39.3$; $p < 0.001$) forms of mTOR in hippocampal homogenates. L-arginine supplementation (group III) effectively increased both the native and phosphorylated mTOR levels ($p < 0.05$ vs. group II). Similar restorative effects on the PI3K/Akt/mTOR axis were observed following fluoxetine treatment (group IV). To provide a comprehensive overview of the pathway activation, we analyzed the ratios of phosphorylated to total protein forms (Table 2). In group II, the p-PI3K/PI3K and p-Akt/Akt ratios were significantly diminished compared to group I ($p < 0.05$). Treatment with L-arginine (group III) significantly increased these activation ratios ($p < 0.05$ and $p < 0.001$ vs. group II, respectively). Interestingly, while native and phosphorylated mTOR levels were restored, the p-mTOR/mTOR ratio in group III showed a significant decrease relative to the depressive model ($p < 0.05$), suggesting a complex modulation of this pathway component (Table 2).

### 3.6. Effect of L-arginine on the mPTP

Based on the observed alteration in hippocampal mitochondrial respiratory chain activities, we further explored the state of the mPTP in depression and assessed the effect of exogenous L-arginine (Fig. 6). In experimental groups I, III, and IV, the mPTP exhibited

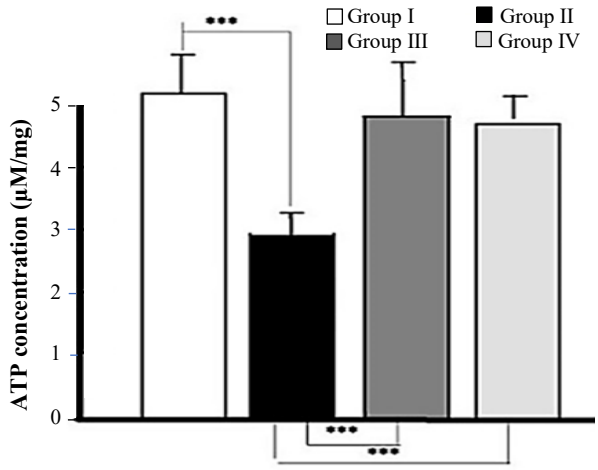


**Fig. 4.** Effect of exogenous L-arginine on ATP levels (μM/mg) in hippocampal cells of depressive rats. Data represent mean ± SEM (n=10 per group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.





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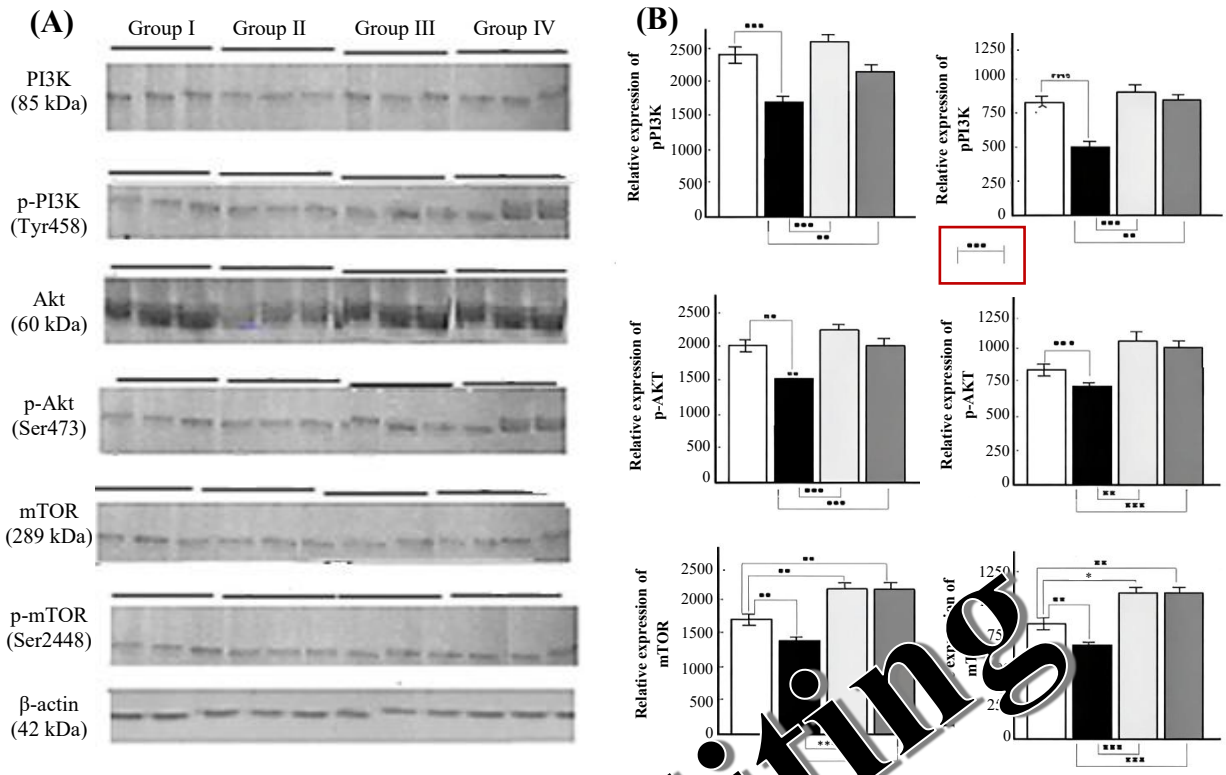


**Fig. 5.** Effects of L-arginine on the activation of PI3K/Akt/mTOR signaling pathway in hippocampus. (A) Representative Western blot bands for total and phosphorylated (p-) forms of signaling proteins. Molecular weights are as follows: PI3K (85 kDa), Akt (60 kDa), mTOR (289 kDa), and β-actin (42 kDa). β-actin was used as an internal loading control to ensure equal protein loading. (B) Densitometric quantification of individual protein expression levels. Data are expressed as mean ± SEM (n =10 per group). Statistical significance: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.



high sensitivity to $CaCl_2$-induced opening, evidenced by a progressive decrease in optical density (Fig. 6A). Conversely, in the depressive group (group II), the mPTP appeared to be in a locked-open state, showing minimal resistance to calcium addition. Upon addition of cyclosporine A, the sensitivity of the pore was successfully modulated (Fig. 6B). Notably, the kinetic data from depressive animals treated with L-arginine (group III) were nearly identical to the control group, indicating effective restoration of pore regulation. Furthermore, the mPTP in group III showed higher sensitivity to cyclosporine-mediated inhibition than that in the fluoxetine-treated group (group IV; Fig. 6B).

## 4. DISCUSSION

Depressive disorder is highly prevalent and constitutes one of the leading causes of disability worldwide. Given the limited efficacy of existing therapeutic options, it is imperative to investigate the molecular underpinnings of the disorder, particularly those related to mitochondrial bioenergetics, to facilitate the development of novel agents with translational potential.

This study examined the antidepressant-like potential of exogenous L-arginine in a corticosterone-induced model, focusing on cellular energy metabolism within total hippocampal homogenates. Depressive states are well-documented to correlate with impaired energy metabolism and reduced ATP levels[21]. L-arginine is deeply implicated in these processes due to its role in the biosynthesis of high-energy compounds like creatine[22]. Consistent with existing literature, our analyses indicated heterogeneous alterations in glycolytic enzyme activities during depressive states, including upregulation of HK as a compensatory response to reduced glycolytic flux[23]. L-arginine administration restored glycolytic throughput, characterized by increased activities of downstream enzymes (Fig. 1). These metabolic disturbances in hippocampal tissue are generally associated with diminished cellular bioenergetics and oxidative stress[24,27-29]. While L-arginine stimulates glycolysis via the creatine/creatine kinase/phosphocreatine energetic-buffering system, its role as a precursor to NO must be noted. While NO is a signaling molecule, its overproduction could potentially contribute to nitrosative stress, highlighting its dual role that warrants careful consideration in metabolic studies.



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**Table 2.** Quantitative analysis of the activation state of each signaling molecule, expressed as the ratio of phosphorylated protein to its respective total protein (p/total).

| Group | p-PI3K/PI3K | p-Akt/Akt | P-mTOR/mTOR |
|---|---|---|---|
| I | 0.32 ± 0.010 | 0.91 ± 0.013 | 2.38 ± 0.21 |
| II | 0.23 ± 0.006*** | 0.50 ± 0.009*** | 2.25 ± 0.11 |
| III | 0.30 ± 0.034## | 0.68 ± 0.01### | 2.0 ± 0.05# |
| IV | 0.39 ± 0.008### | 0.54 ± 0.006# | 1.92 ± 0.03## |

Data are expressed as mean ± SEM (n =10 per group). Statistical significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus the control group (group I); #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ versus the depressive group (group II).

Regarding the mitochondrial respiratory chain, we observed reduced activities of complexes I and III alongside the activation of complexes II and IV (Fig. 2B). While this activation is often interpreted as a compensatory attempt to maintain ATP homeostasis[33,35], it may also reflect mitochondrial dysfunction and pathological electron flow, potentially enhancing reactive oxygen species generation via reverse electron transfer. The normalization of these activities following L-arginine treatment aligns with improved mitochondrial resilience and restored ATP content (Fig. 4)[37-40].

A key finding of this study is the modulation of the PI3K/Akt/mTOR signaling cascade. Depression is associated with one of the pathways in the hippocampus, which contributes to impaired synaptic plasticity[43,45]. Our data showed that L-arginine treatment partially restores the phosphorylation states of PI3K, Akt, and mTOR (Fig. 5). This activation aligns with the observed enhancement in glycolytic flux[48]. Furthermore, L-arginine treatment was associated with maintaining the MPTP in a more closed functional state, protecting against calcium-induced swelling (Fig. 6).

Critically, these biochemical and signaling improvements in the hippocampus were accompanied by the rescue of depressive-like behaviors in our rat model, as evidenced by the FST results. This integration of behavioral and biochemical data provides a more robust confirmation of the efficacy of L-arginine than biomarker analysis alone.

In summary, evidence suggests that L-arginine possesses multimodal actions—including bioenergetic restoration, mPTP stabilization, and PI3K/Akt/mTOR modulation—that correlate with behavioral recovery. While further studies are needed to rule out cell-type-specific effects and the nuances of NO signaling, L-arginine represents a promising candidate for further investigation in antidepressant-like strategies.



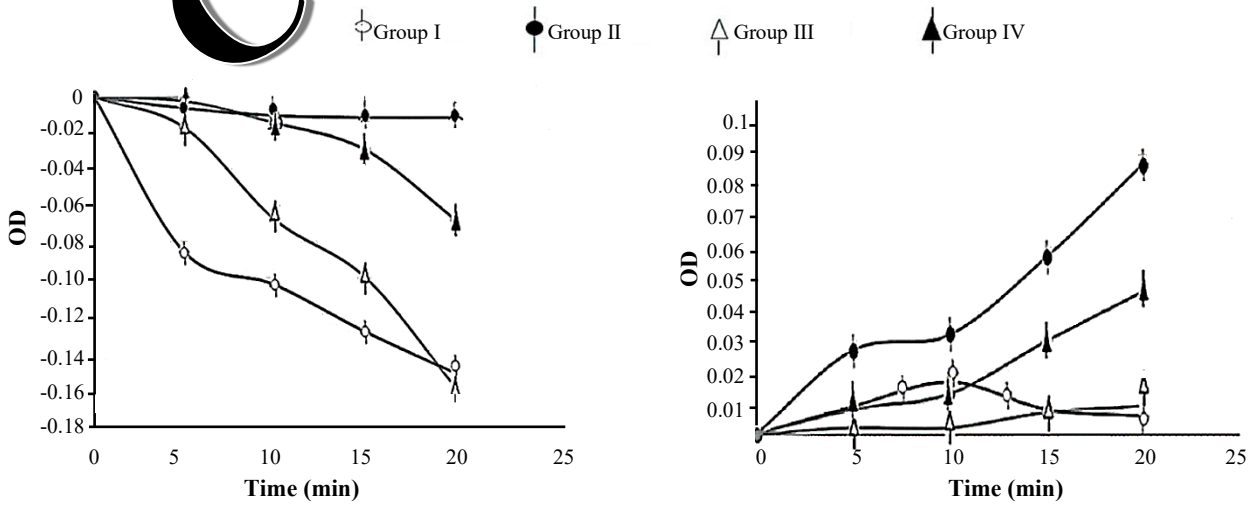


**Fig. 6.** Kinetic analysis of the mPTP state in the hippocampus of depressive rats treated with L-arginine or fluoxetine. (A) mPTP opening dynamics following $CaCl_2$ addition, showing the sensitivity of different experimental groups to calcium-induced swelling. (B) Restoration of mPTP sensitivity following cyclosporine A addition. Y-axis (ordinate): degree of mitochondrial swelling expressed as the change in OD; X-axis (abscissa): experimental time in minutes. Data represent mean ± SEM (n = 10 per group) for group I (control), group II (depressive), group III (L-arginine), and group IV (fluoxetine).



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## 5. CONCLUSION

Our study demonstrates that L-arginine exerts potent neuroprotective and bioenergetic-restorative effects in a rat model of corticosterone-induced depression. We show that exogenous L-arginine effectively reverses the depression-associated decline in hippocampal energy metabolism by enhancing key glycolytic and TCA cycle enzyme activities, thereby restoring ATP production and the creatine/creatine kinase/phosphocreatine energy-buffering system. Furthermore, L-arginine administration modulates mitochondrial resilience by improving electron transport chain function and stabilizing the mPTP. These metabolic improvements are closely linked to the reactivation of the PI3K/Akt/mTOR signaling pathway, which appears to be a central mechanism underlying the ability of L-arginine to restore cellular energy homeostasis and rescue depressive-like behaviors. Collectively, these findings position L-arginine as a promising therapeutic candidate for addressing the bioenergetic deficits underlying depressive disorders.

## DECLARATIONS

**Acknowledgments**

The experimental work was carried out [illegible] the Department of Biology, Faculty of Exact and N[illegible] Sciences, in close collaboration with the Chair [illegible] Biochemistry.

**Generative AI and AI-assisted tech[illegible]logies**

During the preparation of this [illegible]rk, [illegible]e auth[illegible]rs used Gemini (Google) for la[illegible]nguag[illegible]ed[illegible]ng, grammar correction, and basic [illegible]ntr[illegible]t a[illegible]sti[illegible]ts of the figures. The tool was u[illegible]d exclus[illegible]v[illegible] to im[illegible]ove readability and clarity. Hu[illegible]an oversight was strictly maintained throughout the [illegible]cess: [illegible]ll AI-generated suggestions were thoroughly reviewed and verified by the authors, who retain full responsibility for the scientific accuracy, interpretation, and conclusions of the manuscript

**Ethics approval**

The experimental protocol received formal endorsement from the Institutional Review Board at Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia. All animal handling and experimental procedures were performed strictly following the established guidelines for the care and use of laboratory animals. (N58/187).

**Consent to participate**

Not applicable.

**Consent for publication**

All authors reviewed the results and approved the final version of the manuscript.

**Authors' contributions**

TM: investigation and methodology; LN: investigation; MS: investigation; NK: methodology, conceptualization, and writing the manuscript.

**Data availability**

The data that support the findings of this study are available upon request from the corresponding author.

**Competing interests**

The authors declare that they have no competing interests.

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The designated project [illegible]e with the financial support of the Sho[illegible] Rus[illegible]eli Georgian National Science Fou[illegible]ati[illegible] G[illegible]t #[illegible]-7525). Any idea contained in th[illegible]ubli[illegible]tio[illegible] is the authors' property and may [illegible]t r[illegible]sen[illegible]e opinion of the foundation.

**Supplementary information**

The online version contains supplementary material.

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**Supplementary Material (A-10-6570-1)**

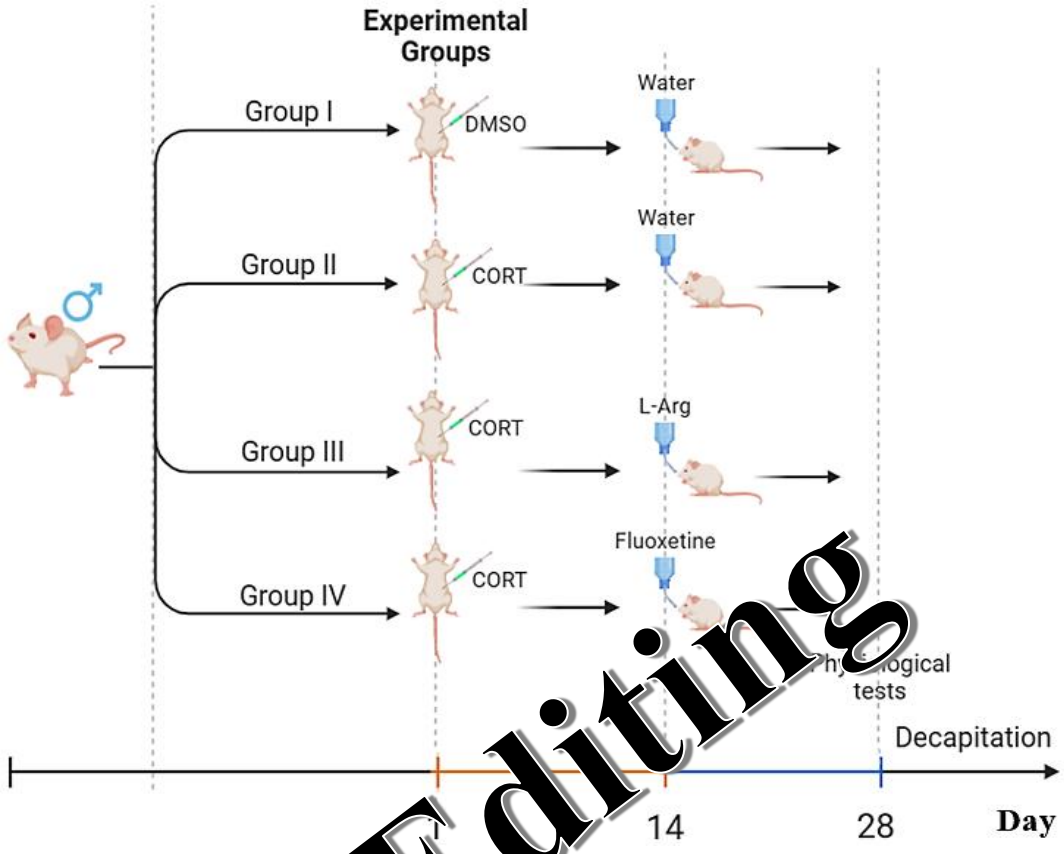


**Fig. S1.** Experimental design and timeline of the study. The scheme illustrates the four experimental groups (group I-IV), the induction of depression via corticosterone, and the 14-day treatment period with L-arginine or Fluoxetine, followed by behavioral testing and decapitation





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