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Original research Article

Neuroprotective effects of atorvastatin and forskolin on hippocampal CA1 region post-global cerebral ischemia in male rats

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Abstract

Objective: Global cerebral ischemia, resulting from reduced blood flow to the brain, often causes significant neuronal damage, particularly in the CA1 region of the hippocampus which plays a critical role in memory processes.

Materials and Methods: Seventy adult male rats were randomly assigned to seven groups (N=10). Group 1 control, while group 2 was the sham group. Group 3 underwent global cerebral ischemia (CI) without treatment. Groups 4 and 5 received CI followed by treatment with forskolin and atorvastatin, respectively. Groups 6 and 7 were treated with two different vehicle solutions following CI. Global cerebral ischemia was created by occluding both common carotid arteries. Forskolin and atorvastatin were administered intraperitoneally 4, 24, and 42 hr post-ischemia in groups 4 and 5. Nissl staining was performed to confirm the induction of CI. The TUNEL assay was used to assess the neuroprotective effects of atorvastatin and forskolin. Cognitive function was evaluated using the Morris water maze test. Data were investigated using one-way ANOVA.

Results: Both atorvastatin and forskolin significantly attenuated neuronal loss and apoptosis in the CA1 region of the hippocampus following CI. Although forskolin consistently showed greater neuroprotective effects across all assessed parameters compared to atorvastatin, these differences did not reach statistical significance, suggesting comparable efficacy between the two treatments.

Conclusion: The results suggest that atorvastatin and forskolin may serve as promising therapeutic candidates for protecting hippocampal neurons and preserving cognitive function after cerebral ischemia.

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Introduction

Ischemic stroke represents a significant global burden, being a primary contributor to both disability and mortality (Achzet et al. 2021). Cognitive impairments, particularly in learning and memory, are commonly observed among survivors of ischemic stroke (Cechetti et al. 2012; Pratiwi et al. 2024).

The bilateral blockage of the common carotid arteries causes global cerebral ischemia which results in targeted damage to neurons that are particularly susceptible (Hedayatpour et al. 2022). The hippocampus, a critical brain region involved in memory and learning, is highly susceptible to ischemic injury, particularly the CA1 region. ischemia–reperfusion events induce significant neuronal damage in this area, leading to impairments in memory-related behavioral functions(Czuba-Pakuła et al. 2025; Lana et al. 2020).

The hippocampus, a critical region for memory and learning, is highly susceptible to ischemic damage. Ischemic events cause neuronal injury within the hippocampus, leading to impairments in memory-related behavioral functions(Mahyar et al. 2025; Nikonenko et al. 2009). Statins, known for their cholesterol-lowering effects, are frequently prescribed to reduce the risk of cardiovascular events and have been reported to affect cognitive performance (Gentreau et al. 2023). The impacts of widely used statins, including simvastatin and atorvastatin, have been extensively investigated in experimental models of memory dysfunction (Don-Doncow et al. 2021).

Studies have shown that treatment with statins after an ischemic injury enhances learning capacity and memory function (Elshafey et al. 2025; Petek et al. 2023) . Studies have demonstrated that forskolin activates adenylate cyclase (AC), leading to an increase in cyclic adenosine monophosphate (cAMP) levels, a key secondary messenger involved in intracellular signal transduction(Insel and Ostrom 2003). In fact, elevated cAMP levels have been shown to enhance long-term memory (Ma et al. 2009).

Forskolin, a natural compound extracted from the roots of *Coleus forskohlii*, has been traditionally used in India, Burma, and Thailand to treat asthma and convulsions, underscoring its long-standing role in traditional medicine. Additionally, forskolin exhibits a neuroprotective effect and enhances cognition(Jain et al. 2025b).

This study aimed to evaluate the effects of atorvastatin and forskolin on CA1 hippocampal neurons, with a focus on comparing their efficacy in mitigating memory impairments induced by ischemia reperfusion.

Materials and Methods

Animal care

All Animals were sourced from the Pharmacology Animal Center of Tehran University of Medical Science. The animals were housed under standardized experimental conditions of a 12:12 hr light-dark cycle and 22–25°C temperature. Animal procedures were approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1395.166).

Experimental groups

Seventy adult male rats weighing 200–250 g were randomly assigned to seven groups (n = 10 per group).

Group 1: Control; No procedures or therapeutic interventions were applied.

Group 2: Sham; Rats were subjected to the same surgical procedures as the ischemia groups, but ischemia was not induced.

Group 3: Cerebral Ischemia (CI); Global cerebral ischemia was induced by occluding the bilateral common carotid arteries for 20 min.

Group 4: CI + Forskolin; Following 20 min of global ischemia under general anesthesia, rats received intraperitoneal

injections of forskolin (20 mg/kg) 4, 24, and 42 hr post-ischemia.

Group 5: CI + Atorvastatin; After global ischemia, rats were administered atorvastatin intraperitoneal (20 mg/kg) 4, 24, and 42 hr following ischemia.

Group 6: CI + Vehicle 1; Rats that underwent ischemia received intraperitoneal injections of DMSO 4, 24, and 42 hr post-ischemia.

Group 7: CI + Vehicle 2; Rats that underwent ischemia were given intraperitoneal injections of saline 4, 24, and 42 hr after ischemia (Figure 1).

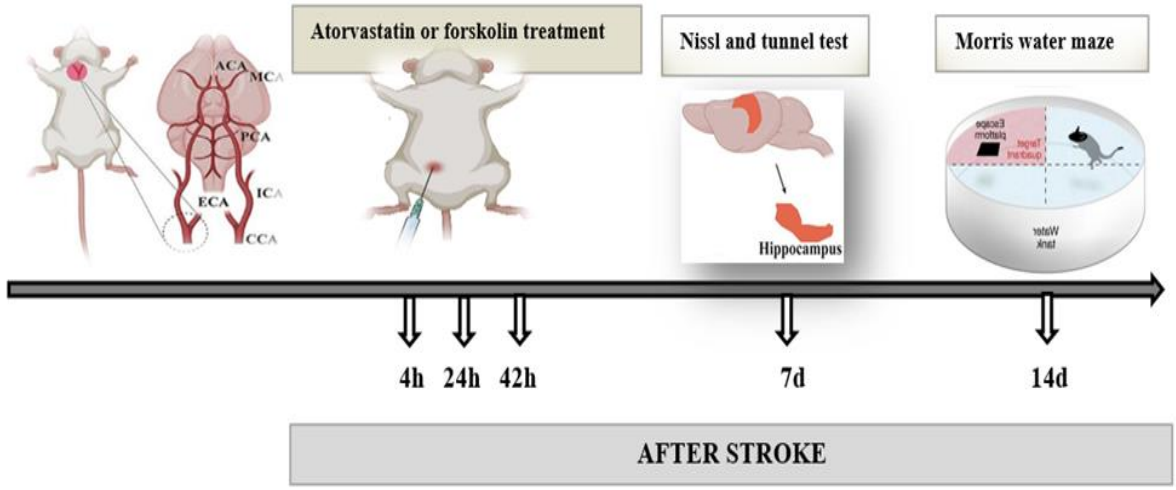


Figure1. Schematic representation of the experimental design. Following ischemic stroke induction, animals received atorvastatin or forskolin treatment at 4, 24, and 42 hours post-stroke. Histological analyses, including Nissl staining and TUNEL assay, were performed on day 7, while cognitive function was evaluated using the Morris water maze on day 14.

Operative protocol

Surgical procedures were carried out under general anesthesia administered via intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). Global cerebral ischemia was induced by temporarily blocking both common carotid arteries for twenty minutes.

Preparation of drugs

Atorvastatin (Sigma Co.), diluted in normal saline, and forskolin, diluted in DMSO, were given intraperitoneally at a dose of 20 mg/kg 4, 24, and 42 hr following the induction of global cerebral ischemia.

Nissl staining

After seven days of treatment with atorvastatin and forskolin, the rats were anesthetized using intraperitoneal injections of ketamine (100 mg/kg) and xylazine (10 mg/kg). Ketamine served as the anesthetic agent, while xylazine served as a sedative to minimize stress. Following anesthesia, the animals were sacrificed via thoracotomy. Perfusion was performed intracardially, first with 120 ml of normal saline to clear the blood, followed by 120 ml of 4% paraformaldehyde for tissue fixation. After perfusion, The brains were gently removed from the skull, and coronal cryosections (30 µm thick) were taken from the hippocampus for further analysis (Hedayatpour et al. 2022).

Morris water maze

The Morris Water Maze (MWM) is a widely used behavioral test for assessing long-term spatial memory in rodents. The apparatus consists of a large circular black tank (183 cm in diameter) filled with water maintained at 24°C. A hidden escape platform (10 cm in diameter) is submerged 2 cm below the water surface in the southeast quadrant of the tank, requiring the rats to locate it during the training sessions.

In the probe trial, the platform remains hidden beneath the water to assess memory retention. In the visible platform task, the platform is elevated 2 cm over the water surface. A recording device connected to a computerized tracking system records and analyzes the animals' movements. The testing protocol included three days of training trials, followed by a probe test on the fourth day. This method was employed to evaluate spatial learning and memory function in rats following CI(Hedayatpour et al. 2022).

Tunnel test

Neuronal nuclear injury was assessed using the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) assay following ischemia. Paraffin-embedded brain sections (3 µm thick) were prepared, with 10 slides per rat. Sections were deparaffinized in xylene, followed by dehydration in ethanol. Subsequently, the sections were rinsed in phosphate-buffered saline (PBS) for thirty minutes at standard temperature and incubated with proteinase K for thirty minutes at 21–37°C to prevent endogenous peroxidase activity. The sections were then incubated with the TUNEL reaction mixture at 37°C for 60 min. After washing with PBS, the slides were treated with converter-POD was applied for 30 min at 37°C in a humidified chamber. Following another PBS wash, 50–100 µl of 3,3'-diaminobenzidine tetrahydrochloride (DAB) was applied, and the slides were rinsed again with PBS. Finally, the sections were mounted and observed under a light microscope at 400× magnification (Shiasi et al. 2018).

Statistical analysis

Statistical analyses were conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for comparisons involving more than two groups. An unpaired Student's t-test was used to compare the two groups. All analyses were conducted using GraphPad Prism software (version 5.0). Data are presented as mean ± SEM, and a p value of less than 0.05 was considered statistically significant.

Results

Forskolin and atorvastatin reduced neuronal damage

Histological examination of the hippocampal region was performed to identify morphological changes following ischemia. Brain slides from the control group displayed intact cell membranes and clearly defined, healthy-appearing nuclei (Figure 2a). In contrast, cells in the ischemia group displayed an unusual appearance with condensed nuclei (Figure 2b).

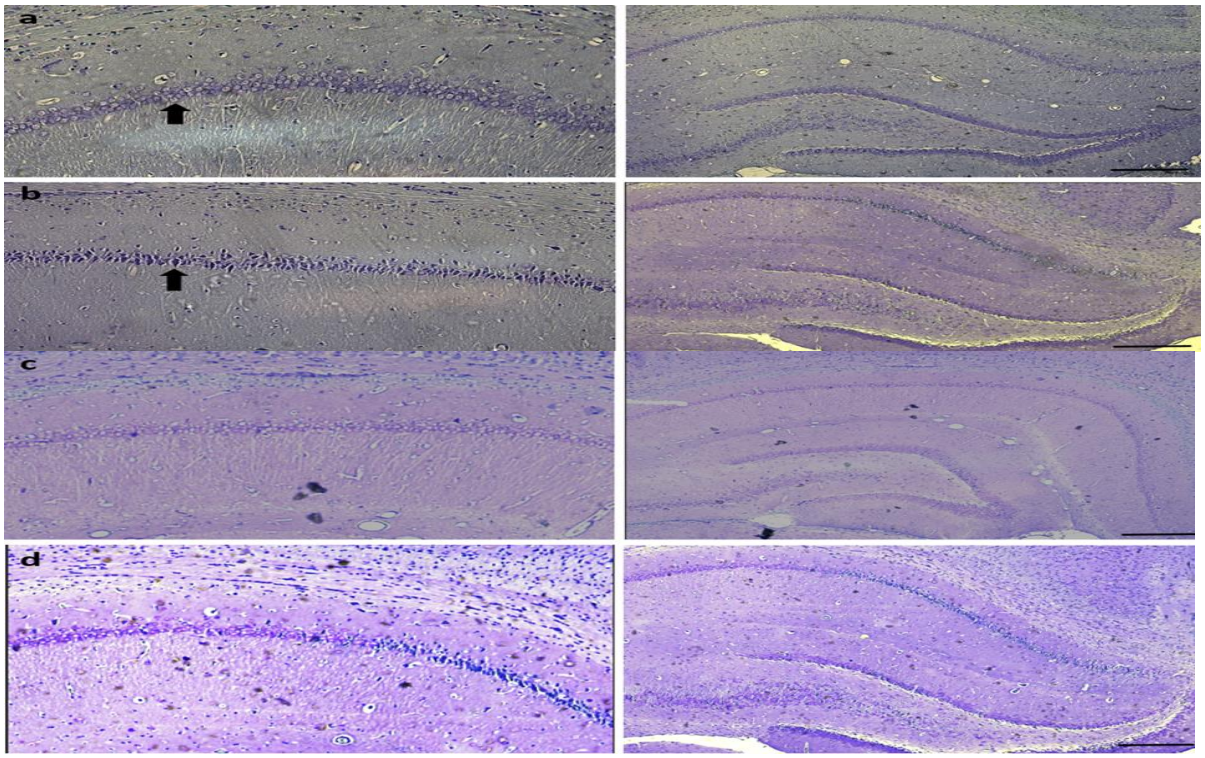
Our results showed a decrease in the number of necrotic cells in the CI+forskolin and CI+atorvastatin groups (Figures 2c and 2d). In contrast, the hippocampus of rats in the ischemia group contained a higher number of larger necrotic cells (Figure 2b) compared to the treatment groups. forskolin was more effective than atorvastatin in reducing necrotic cells. However, no significant differences were observed between the ischemia group and the treatment groups, also between the vehicle and ischemia groups ($p<0.05$).

Tunnel assay

The TUNEL assay was used to assess the degree of apoptosis after ischemic injury. A significant number of TUNEL-positive cells were detected in the ischemia group, indicating increased apoptotic activity (Figure 3b), while no TUNEL-positive cells were observed in the control group (Figure 3a).

Apoptotic nuclei were prominent in the ischemia group, where TUNEL-positive cells displayed an unusual appearance with condensed nuclei (Figure 3b). In contrast, TUNEL-negative cells in the control, CI+atorvastatin, and CI+forskolin groups exhibited Glossy nuclei with undamaged cell membranes (Figures 3a, c, and d).

Administration of atorvastatin and forskolin alleviated neuronal injury and decreased the quantity of injured cells (Figures 3c, 3d). Our findings revealed a significant decrease in the number of normal hippocampal CA1 neurons following ischemia (Figure 3b). However, treatment with atorvastatin and forskolin led to an increase in the number of normal neurons (Figures 3c, 3d). Notably, forskolin treatment after ischemia resulted in a higher number of normal neurons in comparison with the atorvastatin-treated group, although this difference did not reach statistical significance.



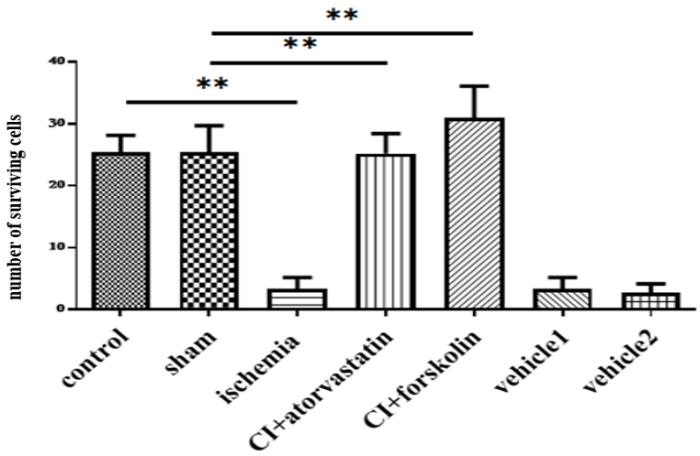


Figure 2. Histological changes in the CA1 region of the hippocampus after ischemia and the therapeutic effects of forskolin and atorvastatin. (a) Control group (n=10): Normal glossy nuclei and intact cell membranes. (b) Ischemia group (n=10): Damaged cells with dense pyknotic nuclei and irregular appearance. (c) Forskolin treatment (n=10): Reduction in the number of necrotic cells. (d) Atorvastatin treatment (n=10): Reduction in the number of necrotic cells. Quantification of surviving neurons in the hippocampal CA1 region. The number of surviving cells was significantly reduced in the ischemia group compared to the control and sham groups (**$p < 0.05$). Both atorvastatin (CI+atorvastatin) and forskolin (CI+forskolin) treatments significantly increased neuronal survival compared to the ischemia group (**$p < 0.05$), with forskolin showing a slightly greater effect. No significant differences were observed between the vehicle-treated groups (Vehicle 1 and Vehicle 2) and the ischemia group. CI: cerebral ischemia. Scale bar = 100 μm.

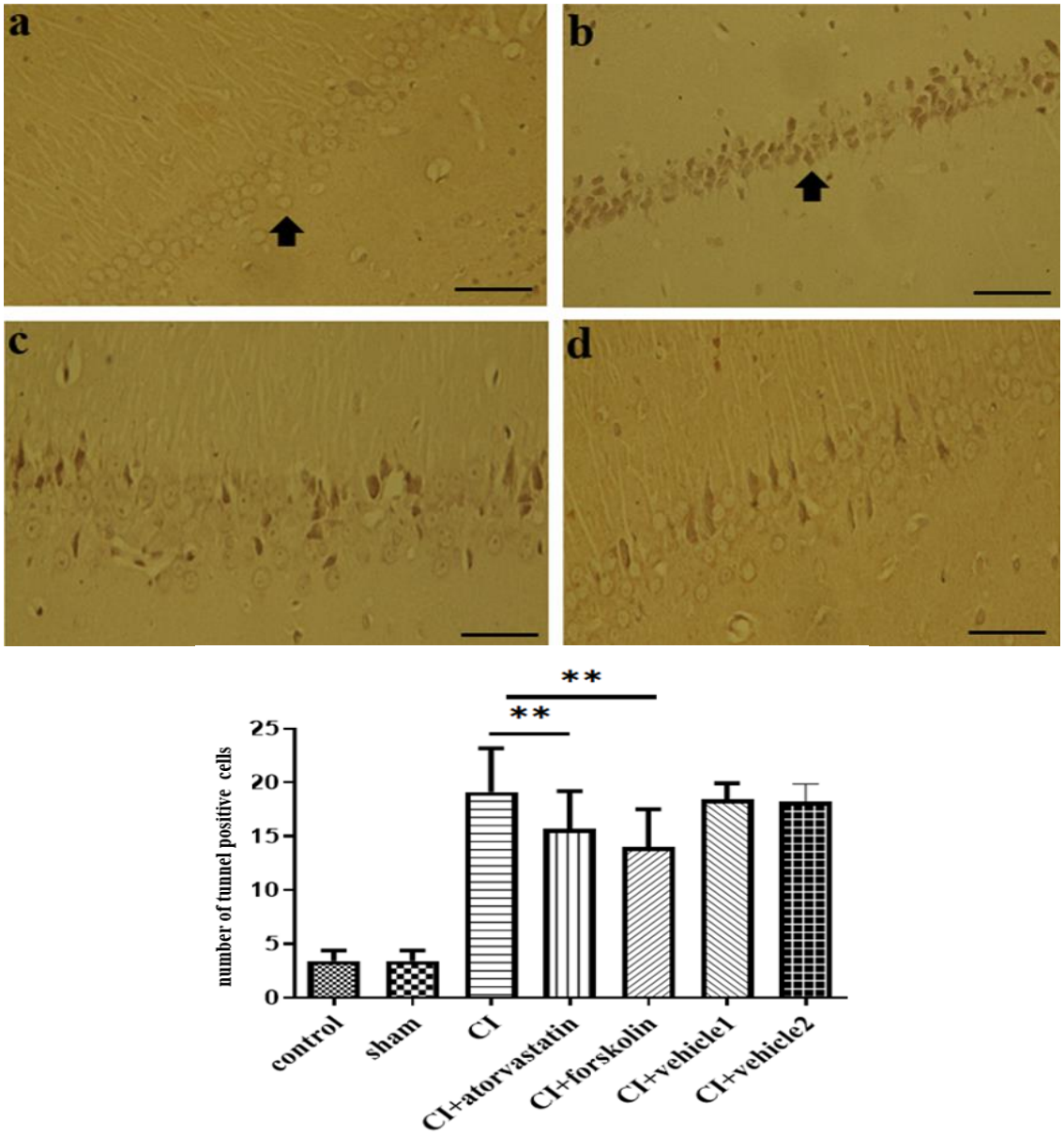


Figure 3. Evaluation of apoptotic changes in hippocampal neurons using the TUNEL assay. (a) Normal hippocampal neurons in the CA1 region (control, n=10) exhibit a regular appearance, while (b) neurons in the ischemic group (n=10) show TUNEL-positive staining, indicating apoptosis. The number of apoptotic cells decreases in the treatment groups: (c) forskolin-treated (n=10) and (d) atorvastatin-treated (n=10), compared to the ischemic group. The diagram shows an increase in the number of TUNEL-positive cells following ischemia. Treatment with atorvastatin and forskolin significantly reduced the number of TUNEL-positive cells. No significant difference was observed between the vehicle group and the ischemic group. **p<0.01 Bar = 100 µm

Atorvastatin and forskolin improved cognitive function

Morris water maze

By day four of the test, the swimming time was substantially longer in the ischemia group compared to the control or experimental groups. The swimming time was substantially shorter in the treatment groups, and it was notably decreased in the forskolin-treated group compared to the atorvastatin-treated group ($p<0.05$; Figure 4). No significant differences were observed between the vehicle groups and the ischemia group.

On day 4, the distance was measured to evaluate the rats' cognitive capabilities. The distance was significantly shorter in the ischemia group compared to the control group ($p<0.05$). No significant difference in distance traveled was observed between the

ischemia and vehicle groups. However, the path length was significantly longer in the CI + forskolin and CI + atorvastatin groups compared to the ischemia group. Additionally, rats in the forskolin-treated group (CI + forskolin) indicated a greater swimming distance compared to the atorvastatin-treated group (CI + atorvastatin) ($p<0.05$; Figure 5).

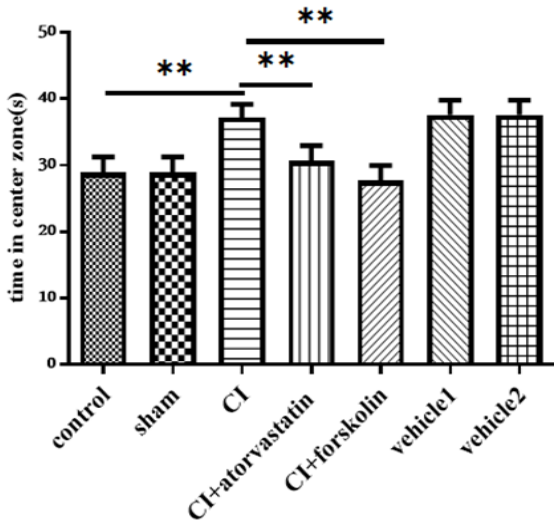


Figure 4. Effect of forskolin and atorvastatin treatment on learning and memory in the water maze. The ischemia group (n=10) took the longest time to reach the platform.Treatment with atorvastatin (n=10) and forskolin (n=10) improved the animal performance, reducing the time taken to find the platform. There is no difference between the vehicle (n=10) and the ischemia group**.** **p<0.05.

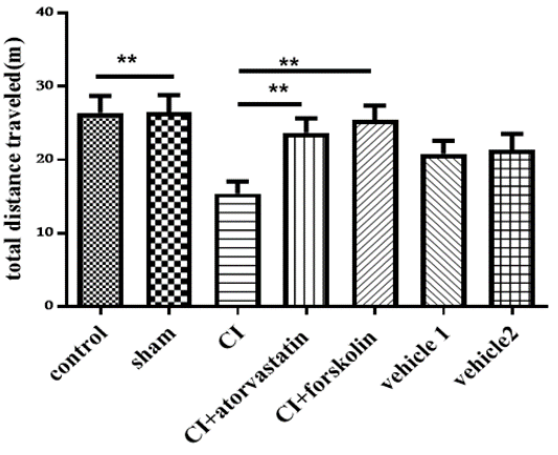


Figure 5. The effect of forskolin (n=10) and atorvastatin (n=10) treatments on learning and memory in the water maze. The distance traveled in the CI group (n=10) decreased, while treatment with atorvastatin and forskolin increased the distance. No significant difference was observed between the vehicle and ischemia groups. **p<0.05.

Discussion

Stroke leads to both physical impairments and cognitive deficits. Approximately 60 to 70% of stroke survivors experience motor dysfunction, as well as impairments in perception, memory, and language (Ma et al. 2009). The hippocampus is a key brain region responsible for learning and memory and is highly susceptible to ischemia-reperfusion injury (Johnson 2023).

In the present study, we evaluated the therapeutic effects of forskolin and atorvastatin on neuronal injury and memory impairment following cerebral ischemia, and subsequently assessed their efficacy. To establish the experimental model, global cerebral ischemia was induced in rats by occlusion of the bilateral common carotid arteries for twenty minutes (Hedayatpour et al. 2022). Histological alterations in the CA1 region of the hippocampus were assessed following ischemia-reperfusion injury. The findings demonstrate that treatment with atorvastatin and forskolin mitigates neuronal damage, thereby protecting hippocampal neurons. These results are consistent with previous studies reporting similar neuroprotective effects(Pordel et al. 2024).

Atorvastatin improved survival outcomes and mitigated cognitive deficits after ischemic injury by suppressing inflammatory cytokine release, decreasing oxidative stress, and inhibiting neuronal cell death in the brain (Tian et al. 2020). Additionally, research have shown that forskolin can decrease reactive oxygen species generation, inflammation, and brain damage (Mehan et al. 2019).

Neuronal damage and death commonly result from cerebral ischemia due to mechanisms such as oxidative stress, inflammatory responses, and apoptosis(Ma et al. 2025). Oxidative stress leads to hippocampal damage and memory deficits (Huang et al. 2025). Based on this, we evaluated neuronal apoptosis in the hippocampus. It is widely recognized that both necrosis and apoptosis can exacerbate

ischemic injury. Injury from ischemia-reperfusion is closely linked to inflammatory responses and apoptotic cell death. In this study, treatment with forskolin and atorvastatin substantially decreased the number of TUNEL-positive cells following ischemia. Moreover, forskolin treatment resulted in a greater reduction in apoptotic cells compared to the atorvastatin.

Forskolin mitigates cell death and apoptosis primarily by elevating intracellular cAMP levels and lowering reactive oxygen species (ROS) production, which underlies its pharmacological actions. Conversely, atorvastatin treatment decreases caspase-3 expression, lessens cell apoptosis, and enhances neurological function. These findings align with those observed in the present study, supporting the role of apoptosis inhibition and neuroprotection (Wang et al. 2024).

Water maze tests were employed to examine the functional outcomes and assess the effects of atorvastatin and forskolin on learning and memory in rats subjected to global cerebral ischemia.

Treatment with atorvastatin and forskolin decreased neuronal damage in the CA1 region and enhanced performance in the water maze test compared with the CI group. Our results demonstrated that CA1 region injury of the hippocampus leads to memory deficits, as assessed by the Morris water maze. Consistent with previous research, we found that treatment with atorvastatin and forskolin enhances memory and improves performance in the water maze test(Wang et al. 2024).

Research has shown that forskolin causes the stimulation of adenylate cyclase(Jain et al. 2025a). Stimulation of adenylate cyclase led to an increase in intracellular cAMP levels, a crucial messenger for intercellular signaling. Increased cAMP enhances memory and cognitive function in rats(Tomczak et al. 2025). Conversely, atorvastatin enhances memory function by reducing oxidative stress and inflammation in the brain (Barone et al. 2011).

Our findings demonstrated that treatment with atorvastatin and forskolin decreased neuronal damage and enhanced cognition ability in comparison with cerebral ischemia group, with forskolin showing greater effectiveness. Notably, rats in the forskolin-treated group exhibited superior performance in the Morris water maze test.

Our study is consistent with previous research investigating the neuroprotective effects of atorvastatin and forskolin on memory and learning, which demonstrated that both compounds effectively improved memory impairment following brain injury(Pordel et al. 2024; Rusciano 2024).

Cerebral ischemia occurs due to the obstruction of a blood vessel supplying the brain, leading to neuronal cell death, apoptosis, and memory impairments. In the present study, treatment with both forskolin and atorvastatin markly reduced neuronal damage in the CA1 region of the hippocampus, decreased apoptosis, and improved memory performance in the Morris Water Maze. Both treatments were effective in mitigating ischemia-induced brain damage. These findings indicate that both agents exert significant neuroprotective effects and may represent promising therapeutic strategies for mitigating ischemia-induced cerebral damage.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Ethical Considerations

All animal procedures were approved by the Animal Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1395.166). and were performed in accordance with the relevant institutional guidelines and regulations. Animals were deeply anesthetized using an approved ketamine–xylazine combination, and euthanasia was performed under this deep anesthesia following institutional and international ethical standards for the care and use of laboratory animals.

Code of Ethics

(IR.TUMS.MEDICINE.REC.1395.166).

Authors' Contributions

A.B.; Designed and Supervised this study. P.M., S.M; Did the tests, Investigated, and Collected data. A.H.; Drafted the manuscript. All authors read and approved the final manuscript.

Abbreviations

CI :(global cerebral ischemia only), DMSO: Dimethyl sulfoxide, MWM: The Morris water maze, PBS: phosphate-buffered saline, POD: peroxidase, DAB: 3, 3'-diaminobenzidine-tetrahydrochloride-dihydrate

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