

The Potential Anti Stress-like Properties of Escitalopram on Improvement of Spatial Memory in Rats Subjected to Predictable and Unpredictable Chronic Mild Stress

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Abstract

Background: Chronic stress and chronic escitalopram usage affect memory. This research examined the potential anti-stress-like properties of escitalopram in improving spatial memory in rats subjected to predictable and unpredictable chronic mild stress (PCMS and UCMS).

Materials and Methods: A total of forty-nine male rats were assigned to various groups: control (Co), sham (Sh), predictable stress (P.St; 2 h daily/21 days), unpredictable stress (UP.St; 2 h daily/21 days), escitalopram (Esc; 10 mg/kg/day for 21 days), and stress groups with escitalopram (P.St-Esc and UP.St-Esc). The Barnes maze test evaluated spatial learning and memory across all groups. Subsequently, the hippocampal weight was measured.

Results: Both the P.St and UP.St groups showed significant ($P < 0.01$ and $P < 0.001$, respectively) improvements in escape latency and traveled distance compared to the control group. It is important to note that only the P.St-Esc group showed decreases ($P < 0.05$ in both) in these variables when compared to the P.St group, whereas no significant differences were found between the UP.St and UP.St-Esc groups. In the P.St and UP.St groups, the left hippocampal weight was significantly ($P < 0.05$ and $P < 0.01$; respectively) lower than that of the control group.

Conclusion: Both PCMS and UCMS adversely affected spatial learning and memory. Additionally, escitalopram improved spatial learning and memory only in rats subjected to PCMS conditions. Therefore, it seems that escitalopram improves learning and memory by different pathways in the PCMS and UCMS conditions. Consequently, it seems that different dosages of escitalopram are required to treat memory deficits due to various types of stress. Left hippocampal atrophy also confirmed the potential role of UCMS conditions in memory impairments.

Keywords: Escitalopram, hippocampus, spatial learning, spatial memory, stress

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INTRODUCTION

In recent times, a considerable number of individuals have been experiencing high levels of various forms of psychological stress, including both predictable chronic mild stress (PCMS) and unpredictable chronic mild stress (UCMS). Chronic stress disrupts homeostasis and leads to physiological and behavioral alterations in brain functions. Therefore, it can induce memory impairment by the activation of the

hypothalamus-pituitary-adrenal axis and the enhancement of glucocorticoids as a stress hormone.^[1-3] It seems that different forms of stress may influence different types of memory in primates.^[4] Although some studies indicate that chronic stress may impede memory and induce hippocampal atrophy, while others propose that it could potentially enhance memory, or have no significant impact on learning and memory.^[5,6]

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Escitalopram is one of the newest and best selective serotonin reuptake inhibitors. It has the potential to reverse learning impairments and enhance memory for 28 days.^[7] In this context, escitalopram is commonly suggested as a first-line treatment for conditions like anxiety, stress, fear, and depression, as well as for its impact on brain function in these disorders,^[8-10] probably due to its mild and tolerable side effects.^[11] Therefore, it has a high rate of prescription. Serotonin is a key neurotransmitter that regulates mood and cognitive function while modulating other neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate.^[12] Since pharmaceutical approaches are regarded as pivotal in stress prevention, changes in serotonin levels play a significant role in memory impairment due to induced stress.^[13,14]

In general, both chronic stress and escitalopram can influence learning and memory.^[15,16] A study provided the first evidence that escitalopram effectively ameliorated tau hyperphosphorylation and the spatial memory deficits induced by PKA activation. These effects do not occur via the anti-anxiety activity of escitalopram but may involve the Akt/GSK-3 β signaling pathway.^[17] Nevertheless, despite extensive research on chronic stress and escitalopram, there is no full information about the role of escitalopram on spatial memory in the comparison of PCMS and UCMS conditions. Therefore, the present study investigated the potential anti-stress-like properties of escitalopram on the improvement of spatial memory in rats under PCMS and UCMS conditions.

MATERIALS AND METHODS

Animals

Forty-nine male rats, each weighing between 200 and 250 grams, were obtained from the animal facility at the Faculty of Pharmacy, Isfahan University of Medical Sciences, Iran. These animals were housed under controlled conditions, with a 12 h light/dark cycle (lights on at 7:00 AM). The ambient temperature was maintained at 23°C $\pm$ 2°C, and the relative

humidity was kept at 55% $\pm$ 5%. Food and water were provided freely, except during periods of stress exposure. Before the start of the experimental procedures, the rats were allowed a week to acclimate to the housing environment. The Animal Use Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.AEC.1401.049) approved all experimental protocols.

The rats were randomly assigned to seven groups ($n = 7$): the Control (Co) group, which was not given any treatment; the Sham (Sh) group, which received the same volumes of saline; and the Escitalopram (Esc) group, where rats were given a daily dose of 10 mg/kg of escitalopram; the Predictable Stress (P.St) group, which was exposed to daily predictable stress; the Unpredictable Stress (UP.St) group, where rats were subjected to unpredictable stress daily; the Predictable Stress with Escitalopram (P.St-Esc) group, where rats received both daily predictable stress and 10 mg/kg of escitalopram; and the Unpredictable Stress with Escitalopram (UP.St-Esc) group, where rats were exposed to unpredictable stress and given 10 mg/kg of escitalopram daily [Figure 1].

Stress paradigm

Chronic mild stress was applied for 2 hours each day from 8:00 to 10:00 AM for 21 consecutive days in both the Predictable Chronic Mild Stress (PCMS) and Unpredictable Chronic Mild Stress (UCMS) conditions. To induce PCMS, each rat was placed in a restrainer.^[5,18] The UCMS was triggered using several stress models, which included restraint (by confining rats in Plexiglas restrainers), sleep deprivation (utilizing a cylindrical clay base with a diameter of 6 cm and a height of 5 cm) placed on the cage floor, away from the food and water sections, cage tilting (by positioning each rat in a cage that is angled at 45°, with food and water located at the elevated end), isolation (by placing each rat in an individual cage), cold exposure (by keeping the rats in plastic cages at temperatures between 2°C and 4°C), raised platform (by positioning rats on a platform approximately 70 cm off the ground), and flashing light (by exposing the rats to a flashing light stimulus of 2.3 volts at a rate of 30 times/min).^[5,19-25]

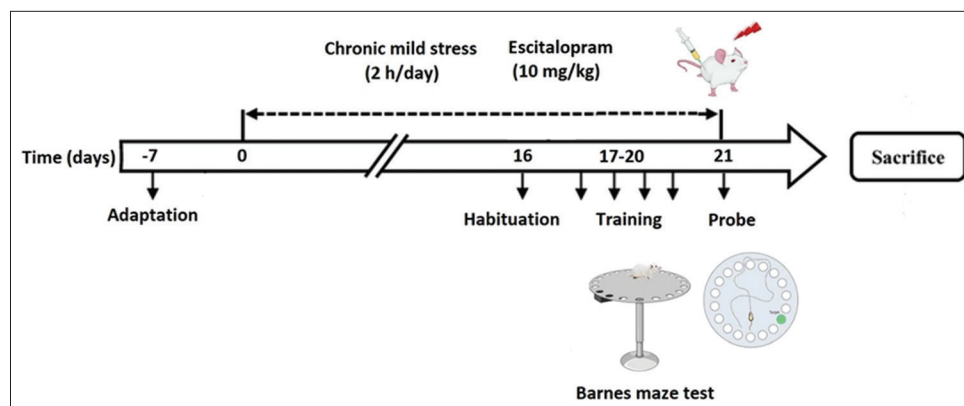


Figure 1: Schematic design of the experimental protocol. Animals experienced chronic stress through both predictable and unpredictable mild stressors, followed by treatment with escitalopram. Ultimately, the rats were euthanized after completing a Barnes maze test, which included habituation, acquisition (training) trials, and a probe trial

Drug treatment

A 10 mg/kg dose of pure escitalopram oxalate powder (Sobhan-Daru, Iran) was mixed with sterile 0.9% saline. Before stress induction, it was administered intraperitoneally (ip) to both stressed and non-stressed rats for 21 consecutive days.^[5,26,27] The selection of a 10 mg/kg dose of escitalopram for this study was based on previous studies and the objective of evaluating its therapeutic effects on stress. In several prior investigations, a 10 mg/kg dose has been used as the optimal dose in animal models (particularly rats) to assess the drug's impact on stress.^[5,26,27]

Barnes maze test

The Barnes maze (BM) apparatus was utilized to evaluate spatial learning and memory in rodents.^[28] The BM apparatus (Tadjhiz Gostar Co., Iran) consisted of a black, circular acrylic platform, 120 cm in diameter and 3 mm thick, positioned 70 cm above the ground. The platform featured 18 holes (10 cm in diameter), evenly distributed along its periphery. One of these holes provided access to a detachable acrylic escape box (12 cm × 23 cm × 12 cm) placed beneath it. Rats were allowed to enter the escape box through this hole. The remaining holes were left uncovered during the experiments.^[29] The maze environment also features various visual cues, such as geometric shapes that are placed at a distance and within view of the rats. These cues are placed permanently on four sides of the table to eliminate the possibility of other environmental cues. Finally, it is imperative to emphasize that the escape box maintains its stability throughout the test.

The animals underwent three phases in the BM test: habituation (1 day), training (or acquisition trials) (4 days, with 4 trials per day, totaling 16 trials), and a probe trial (1 day, 1 trial). Before starting the experiments, the rats were acclimated to the testing environment for 60 min. During the habituation phase (on day 16 of the experiment), rats were positioned in the middle of the maze beneath a transparent glass beaker for 30 s before they were permitted to investigate the platform for 180 s. Once all animals had completed the habituation session, they were brought back to their home cage.

In the training phase, which took place over four consecutive days (days 17–20), rats were individually trained to locate the escape box. For each trial, rats were placed in an opaque cardboard cylinder (20 cm tall, 20 cm in diameter) at the center of the BM for 30 s. This placement allowed the rats to face a random direction when the cylinder was removed and the trial began. Subsequently, the rats were permitted to explore the BM for 180 s. If a rat found and entered the escape box within this time frame, the trial ended, and the rat was allowed to remain in the escape box for 60 s before being returned to the holding cage. If the rat did not find the escape box within 180 s, it was gently guided to the box and allowed to enter it independently. This process was crucial for ensuring that the rats understood the location of the escape box.^[28,30]

On the probe trial (day 21), the escape box was taken away, and the rats were placed in the opaque cylinder at the center of the maze for 30 s. Each rat had 180 s to explore the BM again.

During both the training and probe phases, escape latency and the distance traveled to reach the escape box were recorded using a video camera positioned above the maze. All behavioral data were analyzed using the Neurovision program (Tadjhiz Gostar Co., Iran).

Assessment of hippocampal weight

At the end of the experiments, the left hippocampal weights were measured in all experimental groups.

Statistical analyses

Data are presented as the mean ± standard error of the mean. Latency and distance traveled during both the training and probe phases, as well as hippocampal weights, were analyzed using repeated measures analysis of variance (ANOVA) and One-way ANOVA, respectively. *Post hoc* comparisons between experimental groups were conducted with Tukey's test. All statistical analyses were conducted using SPSS (version 26; PSS Inc., Chicago, Illinois, USA). A *P* value below 0.05 is regarded as statistically significant.

RESULTS

The analysis of data from the control and sham groups showed no statistically significant differences. Therefore, the results from the experimental groups were compared to those of the control group.

Barnes maze test

The escape latency and traveled distance were assessed to observe learning changes over four days. Significant enhancements in both latency and distance were observed in the P.St and UP.St groups compared to the control one ($P < 0.001$ for both). Furthermore, both latency and distance were significantly reduced ($P < 0.05$) in the P.St-Esc group relative to the P.St one [Figure 2a and b]. Additionally, the number of errors during the training phase significantly increased ($P < 0.01$ and $P < 0.001$, respectively) in the P.St and UP.St groups compared to the control group [Figure 2c].

On the probe trial of day 5, both the escape latency and traveled distance were significantly increased in the P.St and UP.St groups ($P < 0.01$ and $P < 0.001$, respectively) compared to the control group. Additionally, the escape latency on day 5 was significantly reduced ($P < 0.05$) in the P.St-Esc group compared to the P.St group [Figure 3a-c]. However, there were no significant differences in the number of errors during the probe phase among the experimental groups [Figure 3c].

Hippocampal weight

The hippocampal weights significantly decreased in the P.St and P.St-Esc groups ($P < 0.05$ in both), as well as in the UP.St and UP.St-Esc groups ($P < 0.01$ in both) compared to the control ones [Figure 4].

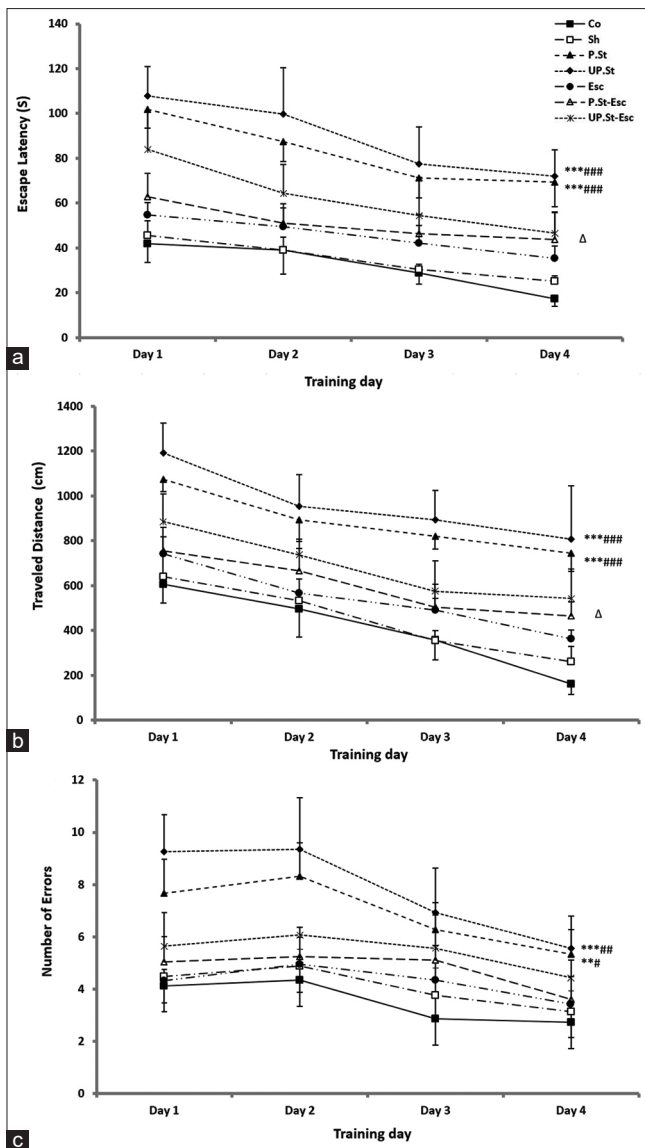


Figure 2: (a) Escape latency and (b) traveled distance, (c) and number of errors made while entering the escape box in the Barrens maze apparatus during the acquisition phase were measured for all groups ($n = 7$). The results are shown as mean $\pm$ SEM, analyzed using one-way ANOVA followed by Tukey's *post hoc* test. Statistically significant differences are indicated as $**P < 0.01$ and $***P < 0.001$ when compared to the Co group; $\#P < 0.05$, $\##P < 0.01$ and $###P < 0.001$ when compared to the Sh group; and $\Delta P < 0.05$ when compared to the P.St group. Co = Control group, Sh = Sham group, P.St = Predictable stress group, UP.St = Unpredictable stress group, Esc = Escitalopram, P.St-Esc = Predictable stress-escitalopram, UP.St-Esc = Unpredictable stress-escitalopram, SEM = Standard error of mean, ANOVA = Analysis of variance

DISCUSSION

This research examined the potential anti-stress-like properties of escitalopram on improvement of spatial memory in rats subjected to PCMS and UCMS.

The findings from the recent research showed a decrease in spatial learning and memory performance under both PCMS and UCMS conditions. Saedi Marghmaleki *et al.*

reported the impairment of aversive memory and long term potentiation in hippocampal CA1 area under both PCMS and UCMS conditions.^[5,27] Some studies demonstrated that spatial and cognitive memories were markedly impaired in stressful conditions.^[5,31] Xu *et al.* indicated that more time is necessary to find the platform in training and probe trials in UCMS conditions.^[31] In contrast, a study suggested that stress hormones may mediate the effects of chronic stress on memory enhancement.^[32] Nevertheless, chronic stress has a complex impact on learning and cognitive functions, which can be both positive and negative depending on the environment, duration, and the type of stressor.^[5,33] The effects of stress on memory formation may hinge on the temporal proximity of stress to encoding, as stress before encoding may enhance subsequent memory formation, whereas stress shortly before encoding may impede it.^[34] Nevertheless, different mechanisms were indicated for memory impairments in chronic stress conditions, including decreased antioxidant, increased inflammatory factors, corticosterone, and glucocorticoid receptors.^[35-39] Some studies indicated that an increase in serum corticosterone levels was one of the most important factors causing brain function impairments in stressful conditions.^[27,40] The hippocampal weight was indicated as a crucial indicator in animal brain studies for evaluating hippocampal atrophy.^[6,41] It was reported that the decreased hippocampal weight and subsequent atrophy may lead to memory impairments in stressful conditions by the increase in stress hormone release.^[1,41,43] Furthermore, chronic stress can be able to affect neural pathways and neurotransmitters, reducing synaptic activity, plasticity, dendritic growth, and neurogenesis within the hippocampus, and affecting the expression of genes involved in learning and memory, such as BCL-2 and BDNF.^[43-47] Saedi Marghmaleki *et al.* suggested that the levels of BDNF and BCL-2 mRNA gene expression in the hippocampus were decreased only in the UCMS conditions, while no such reduction was observed in the PCMS group. This difference may be due to the more severe impact of UCMS on the brain. It seems that there are notable variations in hippocampal gene expression between the PCMS and UCMS groups. However, no significant differences were found in learning and spatial memory performance between the two stressed groups.

According to other recent findings, it was observed that a 10 mg/kg dose of escitalopram enhanced spatial learning and memory, but only in rats subjected to PCMS conditions. However, opinions differ regarding the effectiveness of escitalopram on brain cognition across various contexts.^[16] One study suggested that escitalopram might mitigate stress-induced memory impairments under chronic stress conditions, including both PCMS and UCMSs.^[7,48] Additionally, a prior investigation demonstrated that escitalopram could both prevent and enhance spatial learning and memory in adolescent rats exposed to neonatal stress.^[32] Different mechanisms are suggested for escitalopram actions, it may influence memory by engaging specific signaling pathways to modulate BDNF, serotonin, dopamine, and antioxidant levels; to promote

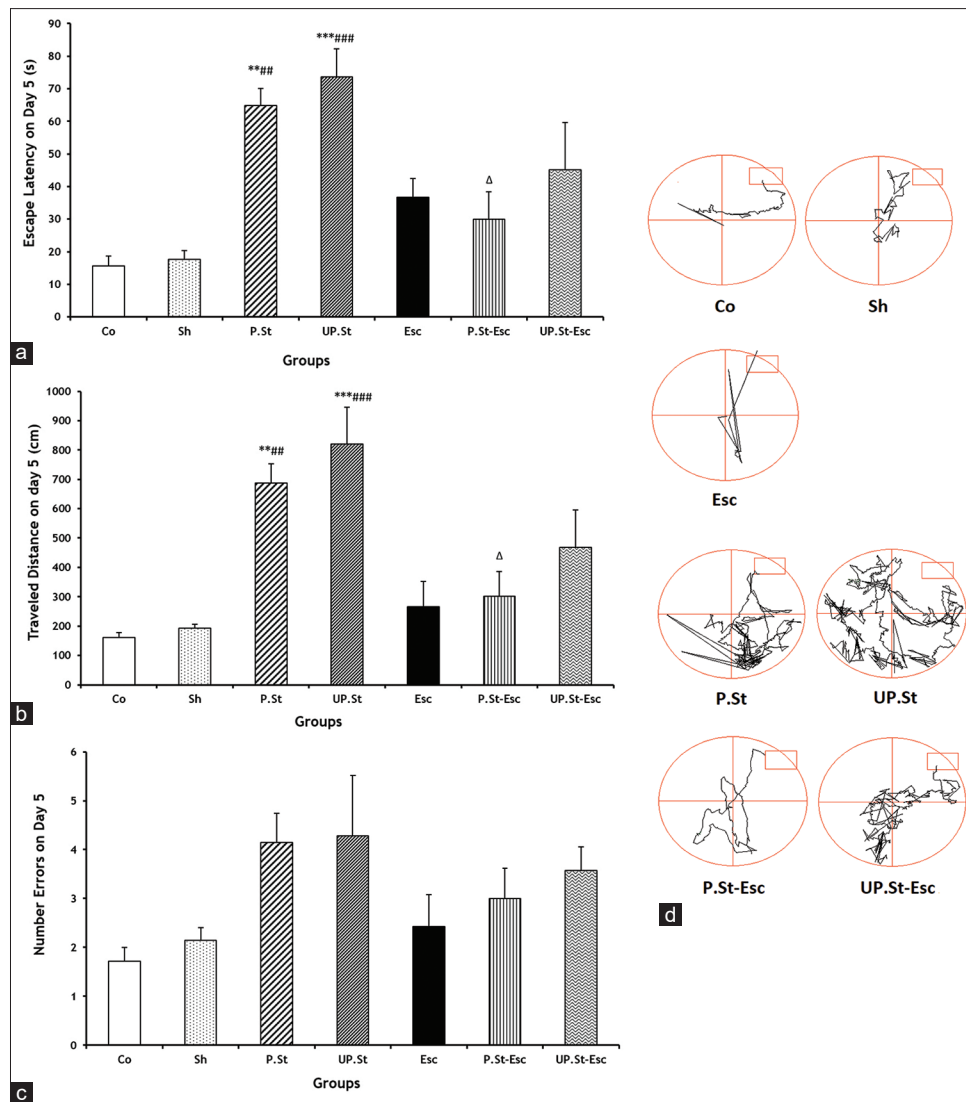


Figure 3: (a) Escape latency, (b) traveled distance, (c) and number of errors made while entering the escape box in the Barrens maze apparatus during the acquisition phase were measured for all groups ($n = 7$). (d) Trace the identification of the escape box in the Barrens maze apparatus during the probe phase for all groups. The results are shown as mean $\pm$ SEM, analyzed using one-way ANOVA followed by Tukey's *post hoc* test. Statistically significant differences are indicated as Results are presented as mean $\pm$ SEM (one-way ANOVA followed by Tukey's *post hoc* test). ** $P < 0.01$ and *** $P < 0.001$ when compared to the Co group; ## $P < 0.01$ and ### $P < 0.001$ when compared to the Sh group; and $\Delta P < 0.05$ when compared to the P.St group. Co = Control group, Sh = Sham group, P.St = Predictable stress group, UP.St = Unpredictable stress group, Esc = Escitalopram, P.St-Esc = Predictable stress-escitalopram, UP.St-Esc = Unpredictable stress-escitalopram, SEM = Standard error of mean, ANOVA = Analysis of variance

cerebral plasticity, augment metabolic capacity, and involve different signaling pathways and receptors.^[8,12,28,43,49-54] For example, certain serotonin receptors such as 5HT₃, 5HT₂, and 5HT_{1A} have been implicated in learning and memory processes that may be differently applied in the PCMS and UCMS conditions.^[26,49,55,56] Additionally, some previous studies reported that escitalopram may influence the expression of genes involved in synaptogenesis and anti-apoptosis, such as the expression of BDNF and BCL-2 in the PCMS and UCMS conditions, probably by activating specific signaling pathways.^[5,32] Based on our previous research, this could be attributed to increased corticosterone levels and alterations in the expression of BCL-2 and BDNF genes under stress.^[5,27]

However, studies on the impact of escitalopram on memory have yielded conflicting results.^[8] Some studies suggested that it may improve memory in chronic stress conditions, while others have found negative effects on cognitive functions.^[57,58] Jensen *et al.* showed escitalopram (10 mg/kg) did not affect memory and cognitive functions.^[59] Therefore, it can depend on the reaction of the type of stress against escitalopram treatment with the same dose of medication. Nevertheless, some have proposed that increased doses of escitalopram might be required to effectively treat memory impairments associated with UCMS conditions.^[60] In the present study, the hippocampal weight did not change by escitalopram administration in normal subjects.

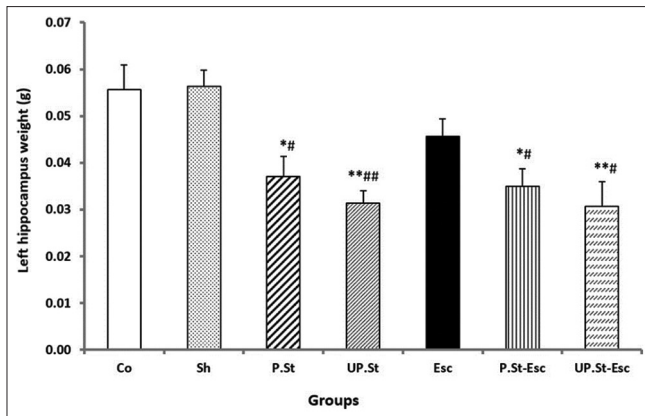


Figure 4: The comparison of various chronic stress protocols and escitalopram on left hippocampal weights (g) in different groups ($n = 7$). Results are expressed as mean $\pm$ SEM (ANOVA test, Tukey's *post hoc* test); * $P < 0.05$ and ** $P < 0.01$ when compared to the control group; # $P < 0.05$ and ### $P < 0.01$ when compared to the Sh group. Co = Control group, Sh = Sham group, P.St = Predictable stress group, UP.St = Unpredictable stress group, Esc = Escitalopram, P.St-Esc = Predictable stress-escitalopram, UP.St-Esc = Unpredictable stress-escitalopram, SEM = Standard error of mean, ANOVA = Analysis of variance

Finally, the administration of escitalopram to the PCMS subjects did not change the error number to find an escape box, despite a reduced latency in reaching the escape box in a similar condition. It was reported that escape latency reflected speed or efficiency and also error number reflected the accuracy of animals in learning and remembering the location escape box in training and probe trials. Therefore, it seems that animals had effectively learned and remembered the correct location of the escape box by escitalopram administration in PCMS conditions, whereas their accuracy in training phases was similar in both PCMS and UCMS subjects. It seems that there were not any differences in spatial learning maps and the accuracy in both PCMS and UCMS subjects by escitalopram. In this way, a study reported that escitalopram can affect both recognition and working memory in rodents.^[8] Overall, the effectiveness of escitalopram learning and memory may be influenced by several factors, including the kind and amount of the medication, treatment duration, the characteristics and length of stress exposure, as well as the age and sex of the individual, the specifics of the task being performed, the method of assessment, the housing conditions of the animals, and the time interval between the cessation of stress and the start of behavioral evaluation.^[42,61-67] Considering the possible variations in intracellular signaling pathways related to PCMS and UCMS, it is suggested to adjust escitalopram dosages to enhance memory under these conditions. A more thorough investigation is needed into the cellular and neurotransmission factors at play, particularly the glucocorticoid, GABA, and serotonin systems, as well as their respective receptors, within both PCMS and UCMS models. Gaining a more profound comprehension of these components and their functions could provide important insights into the processes that regulate brain activity and potentially result in new treatment

methods. In the present study, the hippocampal weight did not change between stress subjects and stress-escitalopram subjects. This lack of protective action may be attributed to the inadequacy of escitalopram's mechanism of action to counteract the neurotoxic effects associated with chronic stress on the hippocampal region.^[68] It was demonstrated that chronic stress induces a series of complex biochemical changes within the brain, which include the dysregulation of both the serotonin and corticosterone systems.^[68] While escitalopram is effective in modulating serotonin levels, it may be insufficient in preventing neuronal damage that arises from excessive hormone secretion.^[43] The limitation of corticosterone remains ineffective in this context.^[69] Consequently, despite its benefits in mood regulation, escitalopram may not entirely mitigate the structural alterations in the hippocampus that are induced by chronic stress. More research is needed to confirm these findings and to further elucidate the complex mechanisms underlying the effects of escitalopram on stress-related outcomes, particularly under different stress conditions.

CONCLUSION

To summarize, both PCMS and UCMS conditions negatively impacted spatial learning and memory. Furthermore, a 10 mg/kg dose of escitalopram improved learning and spatial memory exclusively in rats subjected to PCMS conditions. This observation implies that escitalopram may not uniformly augment spatial memory under stressful conditions. It seems that escitalopram may modulate spatial learning and memory through diverse signaling pathways in the brain in the PCMS and UCMS conditions. As a result, varying degrees of mild chronic psychological stress may require different dosages of escitalopram to potentially improve neural function and memory.

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Conflicts of interest

There are no conflicts of interest.

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