Original Article

Investigating the Mechanisms Involved in Scopolamine-induced Memory Degradation

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ABSTRACT

In the present study, the mechanisms involved in scopolamine-induced memory impairment have been investigated. The molecular events that take place during memory mostly include mechanisms that are seen in the acquisition phase. Results showed that one of the mechanisms of memory destruction caused by scopolamine, in addition to weakening the cholinergic system, is the indirect effect of scopolamine on other neurotransmitter systems, including the glutamatergic system. Scopolamine injection increases dopamine by inhibiting M2/4 muscarinic autoreceptors. These autoreceptors are located on dopaminergic presynaptic neurons, and their activation reduces the release of dopamine. Therefore, blocking these autoreceptors by scopolamine can increase the release of dopamine. Both D1 and D2 receptors are involved in learning and memory processes. In general, stimulation of dopamine D1 receptors follows an inverted U-shaped dose-response curve, meaning that both insufficient and excessive amounts of dopamine cause memory impairment. Therefore, an indirect effect on the dopaminergic system can be one of the scopolamine-induced memory impairment mechanisms. Effects on cell membrane potential and neuron plasticity, and interaction with acetylcholine are among other mechanisms. Serotonin plays a complex role in memory and learning. Serotonin receptors (5-HT2A) also play a role in memory function by affecting calcium transport. This action is similar to dopamine and other G-protein-coupled receptors, which activate phospholipase C, enter calcium into the cell, and activate calcineurin. Activation of 5-HT2A and 5-HT4 receptors by specific agonists of these receptors enhances long-term potentiation (LTP), which plays a significant role in memory. On the other hand, specific 5-HT3 receptor antagonist improves LTP. The 5-HT6 receptor antagonist can improve memory function. Therefore, different serotonin receptors have different roles in memory function, and the interaction between scopolamine and these receptors needs further study. It has been shown that histamine increases the secretion of acetylcholine in the hippocampus, and postsynaptic H1 and presynaptic H3 receptors play a major role in memory and learning; however, whether scopolamine can cause memory impairment through interaction with histamine receptors has been not reviewed.

Keywords: Acetylcholine, Mechanism involved in memory degradation, Non-selective antagonist, Scopolamine

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1. Introduction

Synaptic plasticity is a change in synapse function, and this process is directly related to memory formation. Synaptic plasticity includes short-term changes in the strength of synapse transmission efficiency and long-term changes in the structure and number of synapses (1). Learning induces cellular-molecular changes and ultimately strengthens or inhibits inter-neuron communication. If learning causes changes in the synapse strength of interneuronal circuits, then the maintenance of these changes explains how memories are stored (2). This phenomenon is called long-term potentiation (LTP) and its reverse process, long-term depression (LTD). These two processes cause changes in synapse strength, known as synaptic plasticity (3). In fact, the physical structure of memory can be a form of synaptic plasticity. Today, these two processes are the most important known mechanisms in modulating and regulating synaptic plasticity. It should be noted that LTP in the hippocampus has two stages: Early LTP and delayed LTP. In the initial stage, which lasts for 1-3 h, protein synthesis does not take place (4). If the stimulation is increased, LTP enters a delayed phase that lasts for a longer time, and in this phase, new proteins are made. In contrast to the initial phase, where separate pre- and/or post-synaptic changes occur, the delayed phase requires coordinated structural changes that take place in the pre- and post-synaptic neuron through the activity of forward and backward messengers. Glutamate and NMDA receptors (N-methyl-D-aspartate) are essential for the LTP induction (5,7). Short-term memory causes functional changes in neuronal networks by proper regulation of intracellular messaging systems. These short-term changes can undergo one of two processes: They disappear over time, or they are strengthened and become long-term memory during consolidation process (8). In short-term memory, proteins are affected by post-translational processing and synapse strength changes. While the formation of long-term memory requires the synthesis of new proteins and the development of communication. The molecular processes that are involved in short-term memory include the following (9): Changes in the excitability and exocytosis of the presynaptic neuron, which is carried out due to the change in the conductance of the neuron, which is the result of phosphorylation and calcium influx. Through NMDA receptors in the postsynaptic neuron with the help of calcium/calmodulin kinases (CaMK), protein kinase C (PKC), and tyrosine kinase, it phosphorylates neurotransmitter receptors and causes the production of messengers such as nitric oxide, which is the presynaptic axonal terminal and thus increases the release of neurotransmitters. The activity of the molecules of the signaling pathways remains for a few minutes and creates short-term memory (10,13). It is worth noting that phosphorylation has a half-life that depends on the kinetics of dephosphorylation by phosphatases. The balance between calcium/calmodulin kinase II (CaMKII) and protein phosphatase I (PPI) plays an important role in the formation of short-term memory. (14,15). The molecular mechanisms in each of the stages of memory are as follows:

1.1. Memory acquisition

The molecular events that take place during memory mostly include mechanisms seen in the acquisition phase. For example, LTP, a type of synaptic plasticity, is one of the most important mechanisms. Many studies investigating the mechanisms involved in associative learning have focused on fear conditioning. In fear conditioning, a conditioning stimulus that is initially neutral to the animal (such as a sound) is presented immediately before the unconditioned stimulus (such as an electric shock). The amygdala and the hippocampus are the two main sites involved in this type of learning. At the molecular level, this learning requires NMDA receptors, as deletion of the gene encoding the R1 subunit of NMDA receptors in the CA1 region of the hippocampus causes deficits in associative learning (16).

1.2. Consolidation and memory storage

In addition to NMDA receptors, the consolidation phase is highly dependent on AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor). Therefore, the inhibition of these receptors in the stabilization phase causes disruption in recalling information (17). The PKA plays a key role in the creation of CREB transcription factors in cascade events that cause gene expression and synthesis of new proteins during acquisition and stabilization stages. Therefore, the stabilization phase initiates a wave of protein synthesis and gene expression (Figure 1). Different signaling pathways are activated with distinct time periods during the stabilization phase. For example, it has been found that the ERK/MAP kinase cascade, which is important for LTP, is activated in the amygdala 60 minutes after fear conditioning, and PKA activity and phosphorylated CREB (p-CREB) levels are increased 3 and 6 h after training, respectively (18).

1.3. Decreased glucose metabolic rate

Glucose is necessary for the normal functioning of the brain, and it has been shown that the injection of an excessive amount of glucose can improve memory and learning and can reduce amnesia caused by scopolamine. Researchers have suggested that glucose may increase the availability of acetyl coenzyme A, an essential coenzyme in glucose synthesis. Scopolamine can cause memory impairment by reducing glucose uptake by the brain. In addition, scopolamine can reduce cerebral blood flow, which may contribute to the reduction of glucose uptake. The

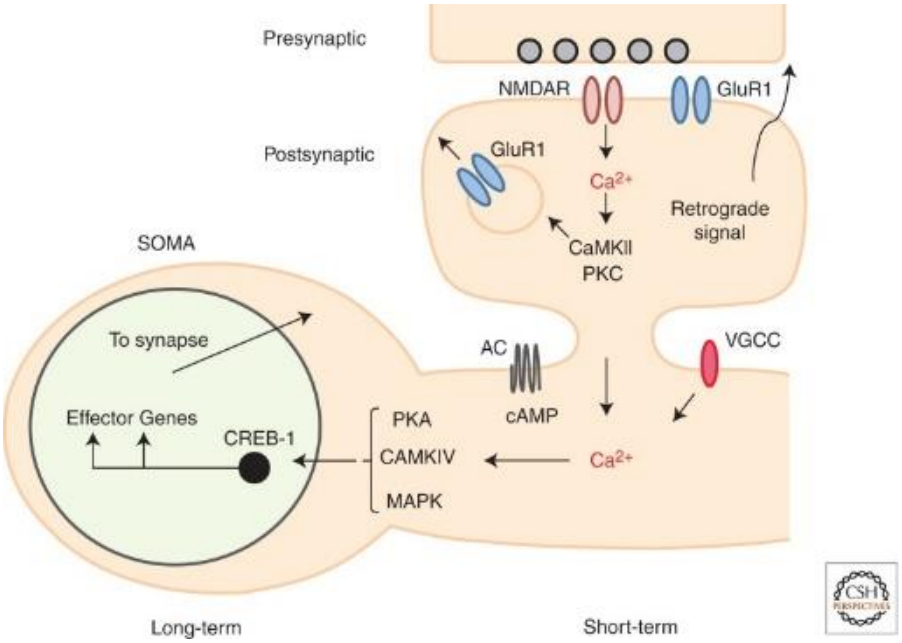

Figure 1. Molecular mechanisms for the induction of LTP and memory. Short-term plasticity (lasting a few hours) is caused by Ca^{2+}-dependent NMDAR signaling to protein kinases and recruitment of new glutamate receptors to the synapse. Long-term plasticity (lasts for days) requires CREB-dependent gene activation in the nucleus by the action of several protein kinases. Long-term plasticity and memory also require the synthesis of a constitutively active isoform of PKC

mechanism of action of glucose in improving memory and learning performance is under more detailed investigation (19). Based on the investigations, very few studies have evaluated the effect of gummosin on various biological processes, especially on memory and learning. The only study that investigated the effects of gummosin is the study by Iranshahy et al. in 2019, which investigated the cytotoxic effects of this compound on breast and prostate cancer cell lines (20). Therefore, studies related to the effects of the Ferula plant and its coumarin derivatives on memory and learning are examined:

1. Vijayalakshmi et al, in 2012 (India), in a study titled the effect of the gum extract of *Ferula asafetida* Linn, investigated learning and memory in Wistar rats (Evaluation of the effect of Ferula asafoetida Linn. gum extract on learning and memory in Wistar rats). Extract produced significant improvement in memory score i.e. step through latency at 400 mg/kg dose in passive avoidance model ($P< 0.05$) and dose-dependent improvement of transfer latency in elevated plus maze model ($P< 0.001$). Dose-dependent inhibition of brain cholinesterase ($P< 0.001$) and significant improvement in antioxidant levels ($P< 0.05$) were also noted. Dose-dependent inhibition of brain cholinesterase ($P<0.001$) and significant improvement in antioxidant levels ($P<0.05$) were also observed. The results revealed that the memory enhancement potential of F. foetida can be attributed to the inhibitory properties of acetylcholinesterase and antioxidant properties. Hence, the use of F. foetida in the diet is beneficial and can also be used as an adjunct to existing anti-dementia treatments (21).

2. In a study by Narayanan et al. in 2017 (India), titled the psychopharmacological profile of the effects of *Ferula asafoetida linn*. It was investigated in mice using MazY, EPM, and Open field devices. A dose of 400 mg/day of *Asafoetida* orally improved memory compared to 200 mg/day in rats. *Asafoetida* showed greater power in improving memory than Donepezil and Vitamin C. After 11 days of daily treatment with commercial *Asafoetida* powder, more than 50% of the mice showed an increase in recognition index compared to 0.55 at the beginning. The results showed that *Asafoetida* powder has a nootropic effect in a mouse model (22).

3. Phytochemical analysis, anticholinesterase, *in vitro* antioxidant activity, and *in vivo* nootropic effect of *Ferula ammoniacum* (Dorema ammoniacum) D. Don in Scopolamine-Induced Memory Impairment in Mice (in a study by Nazir et al. 2021). It was investigated in scopolamine-induced memory impairment in mice. Ethyl acetate (Fa. EtAc) and chloroform (Fa. Chf) fraction extracts more potently inhibited AChE and

BChE with IC50 values of 40 and 43µg/ml and 41 and 42µg/ml, respectively. Similarly, the highest free radical scavenging potential was exhibited by Fa. EtAc against DPPH (IC50=100µg/mL) and ABTS (IC50=120µg/mL). Extract doses of 100 and 200mg/kg body weight significantly (P<0.01) improved short-term memory by increasing the percentage of spontaneous alternation in the Y-maze test along with increasing the discrimination index in NORT, which clearly indicated an increase in the recognition memory of rats. The results indicated that the extracts more powerfully destroy the tested free radicals, show anticholinesterase activity, improve learning abilities, and reduce scopolamine-induced memory impairment in a mouse model. Thus, it reveals that these extracts can be effectively used to manage oxidative stress, neurodegenerative diseases, neurological diseases, and memory loss (23,24).

4. In a study conducted in 2003 by Saya et al. entitled (Anticonvulsant effect of *Ferula gummosa Boiss* extract against experimental seizures), anticonvulsant activities, neurological defects, and lethality of the root extract of this plant were investigated in mice. In the said study, *Ferula gummosa* extract showed dose-dependent prevention of pentylenetetrazol-induced tonic seizures. Preliminary phytochemical analyses showed the presence of terpenoids, alkaloids and a small amount of cardenolide in the extract. It seems that the anticonvulsant and neurotoxic effects of the extract are partially related to the terpenoid compounds. The results concluded that the extract of *Ferula gummosa* Boiss calms and reduces seizures in mice and improves brain function (25).

5. A study conducted in 2017 by Sadeghnia et al. titled (Effects of *Ferula gummosa* standardized extract on glutamate-induced neurotoxicity). In this research, the neuroprotective effect of *Ferula gummosa* root extract against oxidative stress caused by glutamate was investigated in rat adrenal pheochromocytoma (PC12) and mouse neuroblastoma (N2a) cell lines. Cells were pretreated with the extract for 2 h and then exposed to glutamate for 24 h. After 24 h, the levels of malondialdehyde (MDA), reactive oxygen species (ROS), and apoptotic cells were determined in both cell lines. The results showed that glutamate increased lipid peroxidation, ROS, and apoptotic cells in both cell lines. The extract significantly increased cell viability and reduced ROS production under glutamate-induced oxidative stress in these cells. Furthermore, the extract decreased the level of MDA and apoptotic cells. The results showed that *Ferula gummosa* root may have a protective effect on glutamate-induced toxicity, indicating that this extract protects neurons from glutamate-induced oxidative stress (26).

2. Materials and Methods

In the present study, 65 male Wistar rats with an approximate weight of 200-250 g were purchased from the Pasteur Institute in Tehran and transferred to the animal shelter of Shahrekord University of Medical Sciences, Shahrekord, Iran. Then, they were randomly divided into 13 groups, and each group was separately kept in a cage. The rats were kept at a temperature of 21-23°C and under a regular 12-h light-dark cycle, and there was free access to food and water except during the experiment and they were checked by the researcher before the experiment. It should be mentioned that each rat was used only once. In addition, the effect of gummosin on tissue parameters (counting the number of neurons), hippocampal field synaptic potential of the brain by the LTP method, and the expression of *NMDA* and *CREB* genes were evaluated. The histology of CA1 and CA3 regions in different groups during the experiments, working with laboratory animals, surgery and brain extraction, and the ethical principles of working with laboratory animals with the Code of Ethics IR.IAU.FALA.REC.1401.018 were according to the instructions.

2.1. Recording the field synaptic potential of the brain hippocampus by LTP method

Initially, the animals were anesthetized by intraperitoneal injection of ketamine and xylazine (ketamine 90 and xylazine 10 mg per kg of body weight). Then, the animals were placed in the stereotaxic apparatus. The body temperature was kept constant at around 35.5 to 36.8. Then, by creating a longitudinal slit in the posterior part of the head, the surface of the skull was highlighted with two reference points, Bregma and Lambda. With the help of a dental drill, two holes for stimulating and fixation electrodes were created in the skull, and a bipolar stimulating electrode (DV=2.3mm, ML=3.4, AP=-1.8) made of stainless steel with an insulating coating (with a diameter of 0.125mm) whose only cross-section was conductive was placed in the Perforant Pathway (PP) of the brain and a stability electrode (DV= 2.3-7.2mm, ML=3.2, AP=-8.3) made of tungsten with an insulating coating which only cross-section was conductive and placed in the granular cells of the dentate gyrus. To prevent damage to the brain tissue, the electrodes entered the brain very slowly. Field potential recordings were made from granular cells of the dentate gyrus following PP stimulation. The synaptic field potential was amplified by a Science Beam differential amplifier (1000×) and a filter (Band pass 1Hz and 3KHz). The signals obtained from the neural electrical activity tracking system were transferred to the computer and calculated and processed by Science Beam Electro module software (version 12),

the slope of the curve, the area under the curve, and the amplitude of cumulative field potentials (fEPSP) and compared in different groups. Stimulation intensity was set to about 40% of the maximum fEPSP response and field excitatory postsynaptic potential (fEPSP). The amplitude and slope of cumulative potentials (PS) were measured. Stimulus-response function or Input/Output (I/O) was obtained to evaluate the synaptic power by changing the current intensity from 50-1000 microamperes and the average of five responses obtained from each current intensity was taken. After the stabilization of the basic response, LTP was induced with a frequency of 400Hz and an intensity that produced 80% of the maximum response, and the responses were recorded at the desired times to investigate synaptic plasticity (15).

2.2. Investigating gene expression with Real-Time PCR test

In the present study, the expression of *NMDA* (Nr2B and Nr2A) and *CREB* genes in the hippocampus of the studied groups was evaluated using Real-Time PCR. From each RNA after reverse transcription, 1 microgram of qRT-PCR of *NMDA* and *CREB* genes were extracted by mRNA. Changes in hippocampus levels were measured using Invitrogen's (TRIzol) reagent from total RNA. We also measured the level of calcium in the brain tissue of mice. Calcium was measured in the blood and brain tissue. That is, before the mouse was killed, this level of calcium was measured in the blood and brain tissue. Spinning conditions were measured using the reagent after reverse transcription of 1 µg of RNA from each sample using the PrimeScript RT reagent kit. Thermal cycling conditions included an initial activation step for 30 s at 95°C, followed by 45 cycles, including an annealing step for 5 s at 95°C and a combination step with extension lasting for 20 s at 60°C. Melting curve analysis was used to validate whether all primers produced a single PCR product (15).

2.3. Counting the number of neurons in the hippocampus of the brain

We dissolved 0.1 mg/kg of cresol violet acetate powder in 100 cc of distilled water; after it was completely dissolved, we added about 0.3 ml of acetic acid. First, the rat brain was removed from the skull and kept in 10% formalin for cutting the brain tissue; then, the brain tissue was cut into pieces with a thickness of 5 µm using a microtome (Leitz 1512 Germany). Then, the prepared slices were deparaffinized, and after placing the slices in xylene and alcohol, the tissue samples were hydrated and after washing in ordinary water and distilled water, they were stained with cresol violet acetate. Then, after washing and dewatering with distilled water and passing through the xylene solution with Antlan glue, a slide was glued on the slide (15). Stained tissue sections were used to count the number of neurons in the hippocampus of the CA1 and CA3 parts of the brain and were examined under a light microscope (microscope connected to a camera) in terms of the diameter and number of dead neurons.

3. Results

3.1. Long-term synaptic plasticity (LTP)

The LTP is the electrophysiological mechanism of memory that was evaluated after applying HFS in the CA1 region of the hippocampus, and the average amplitude of fEPSP for 60 min after HFS was compared to the Base period in all groups (Figure 3). The HFS caused a significant increase in the fEPSP amplitude compared to the baseline level in the control group (259.1±22.6%); however, the LTP induction amplitude in the scopolamine group (134.6±9.24%) was significantly lower than the control group ($P<0.001$). However, the amplitude of LTP induction in the Sco+Gum10 group reached the normal level (201.8±18.23) and showed no difference with the control group. In addition, LTP was induced in the Sco+Gum20 (231.5±17.61%) and Sco+DP (234.7±17.08%) groups as much as in the control group, and the LTP induction range in both groups showed a significant difference compared to the scopolamine group ($P<0.01$; Figure 2).

3.2. Results of Real-time PCR studies

3.2.1. Effect of Gummosin administration on *CREB* gene expression

Figure 3 displayed the expression level of *CREB* gene mRNA in the hippocampus. As shown in Figure 3, the CREB mRNA expression level in the scopolamine group (0.14±0.07) compared to the control group (1.65±0.32) reveals a significant decrease ($P<0.01$). The Sco+gum10 (0.31±1.06), Sco+gum20 (0.38±1.16), and Sco+DP (0.24±1.36) groups do not show significant differences with the control group.

3.2.2. Effect of Gummosin administration on *NR2B* gene expression

The effect of gummosin administration on *NR2B* gene mRNA expression is shown in Figure 4. The expression level of NR2B mRNA in the scopolamine group (2.11±0.52) compared to the control group (0.42±0.23) shows a significant increase ($P<0.01$). Administration of gummosin with a dose of 10 has decreased the expression of NR2B mRNA in the Sco+gum10 group (1.11±0.33) so that it does not show any difference with the control group. While treatment with gummosin with a dose of 20 in the Sco+gum20 (0.49±0.10) and Sco+DP (0.202±0.57) groups caused a significant decrease in the mRNA expression of this gene compared to the scopolamine group ($P<0.01$).

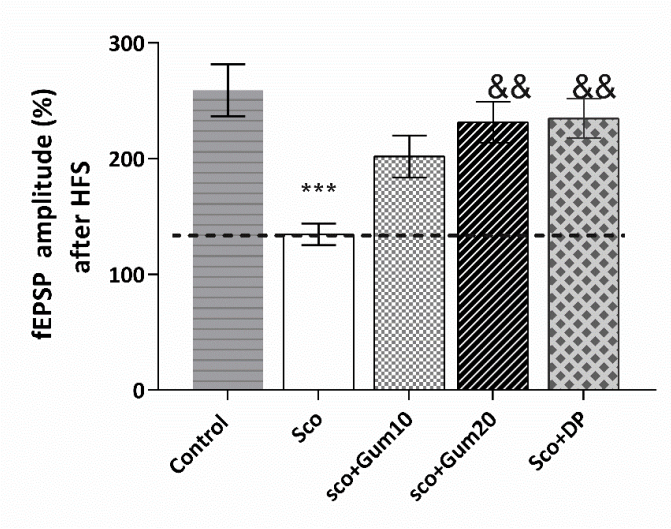

Figure 2. The effects of gummosin administration on the average percent change in fEPSP amplitude after HFS in memory impairment model rats. LTP induction did not occur in hippocampal rats of scopolamine group, but the administration of gummosin and donepezil 2VO+ESC2 improved LTP induction to the control level. The data are expressed as Mean ± SEM. P<0.001***, compared with the control group, compared with the scopolamine group &&P<0.01

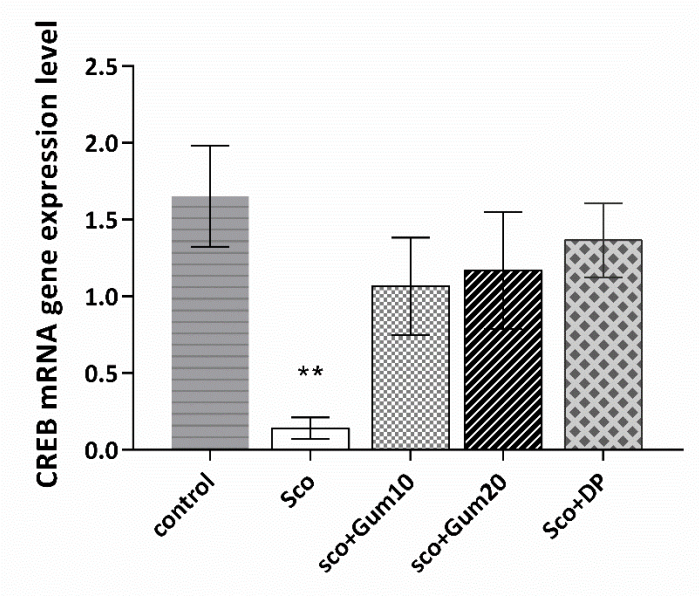

Figure 3. Evaluation of the effect of Gummosin administration on CREB gene expression by QRT-PCR. **P<0.01, compared with the control group

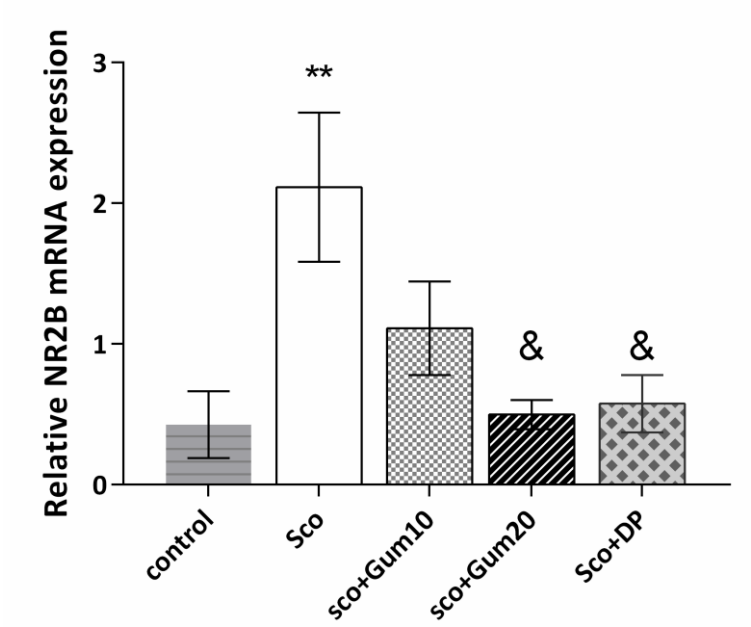

Figure 4. Evaluation of the effect of gummosin administration on NR2B gene expression by QRT-PCR. P<0.01**, compared with the control group. P<0.05 & compared with Sco group.

3.3. Effect of Gummosin administration on *NR2A* gene expression

As Figure 5 displays, the mRNA expression level of the *NR2A* gene in the hippocampus of scopolamine group rats (0.14±0.36) compared to the control group (1.65±0.31) has decreased significantly (P<0.05). The groups receiving gummosin10 (0.24±0.50) and Gummosin20 (1.14±0.12) did not show significant differences compared to the control group. The Sco+DP group (1.54±0.20) showed a significant increase in NR2A mRNA expression compared to the scopolamine group (P<0.05).

4. Discussion

4.1. Estimating the number of neurons in the CA1 area

The total number of neurons in the CA1 region in the scopolamine group was reduced by 36% compared to the control group (P<0.001). However, treatment with Gummosin20 prevented the decrease in the number of neurons, so that the number of neurons in this group does not show a difference with the control group. In addition, treatment with donepezil showed a significant difference in the scopolamine group (P<0.05; Figure 6).

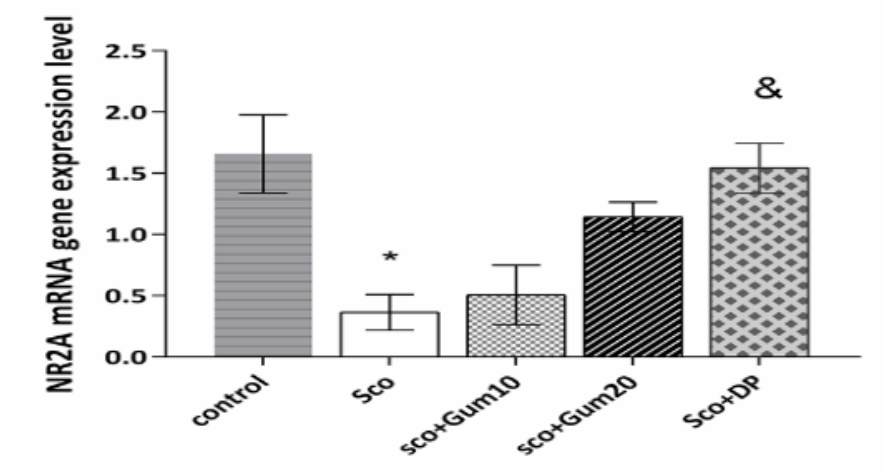

Figure 5. Evaluation of the effect of gummosin administration on NR2A gene expression by QRT-PCR P<0.05*, compared with the control group. P<0.05# compared with Sco group.

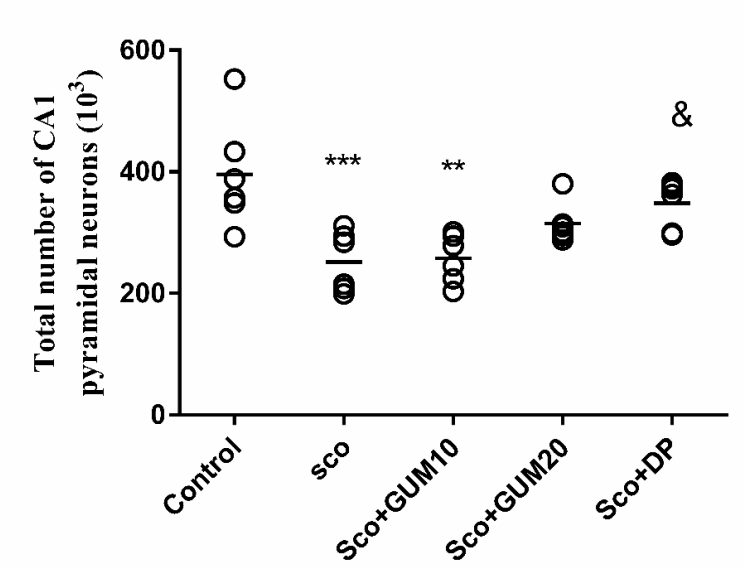

Figure 6. Dot plot of the total number of neurons in the CA1 region in different groups. Each point represents a parameter in an animal. The horizontal bar shows the average parameters of each group. P<0.001 ***, P<0.01 ** compared to the control group, & P<0.05 compared to the scopolamine group.

4.2. Estimating the number of neurons in the CA3 area

The effect of gummosin administration on the total number of CA3 neurons is shown in Figure 7. Compared to the control group, the number of CA3 pyramidal neurons in the scopolamine group was significantly lower (P<0.0001). the Sco+DP group showed a significant difference with scopolamine group. The total number of CA3 pyramidal neurons in the hippocampus in the gummosin 10 and gummosin 20 groups showed a significant difference compared to the control group (P<0.05).

4.3. Comparison of histological studies

4.3.1. Hippocampus histology

The histology of CA1 and CA3 regions in different groups is shown in Figure 8. There were no significant changes in the histological appearance of the CA1 region of the control group compared to the Sco+DP and Sco+Gum20 groups. However, this area in the scopolamine and gummosin10 group showed less cell population and smaller and pyknotic neurons compared to the control group. These changes seem to be improved in the group receiving Gummosin20. As Figure 8 exhibits,

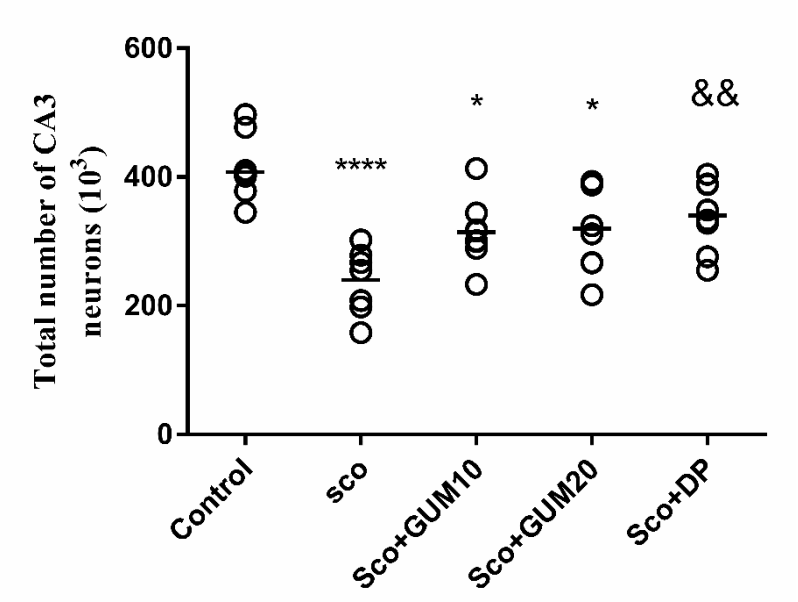

Figure 7. Dot plot of the total number of neurons in the CA3 region in different groups. Each point represents a parameter in an animal. The horizontal bar shows the average parameters of each group. P<0.0001 ****, P<0.05 * compared with control group, & P<0.01, compared with scopolamine group.

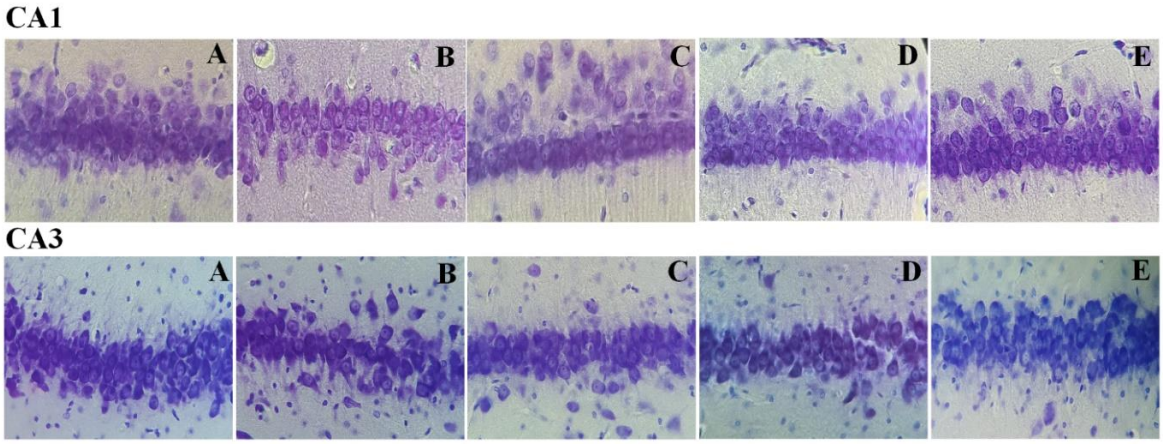

Figure 8. Histological evaluation of CA1 area in the control (A), scopolamine (B), low dose gummosin (C) and high dose Gummosin (D) and donepezil (E) groups.

Gummosin showed no improvement effect on CA3 area in two groups Sco+Gum10 and Sco+Gum20. The histological appearance of the CA3 region in the Sco+DP group does not show any difference with the control group.

Effect on the glutamatergic system: It seems that one of the mechanisms of memory destruction caused by scopolamine, in addition to weakening the cholinergic system, is the indirect effect of scopolamine on other neurotransmitter systems, including the glutamatergic system. Studies have shown that the antagonist of NMDA receptors, MK801, in a dose-dependent manner leads to a decrease in learning and memory, which indicates the involvement of the hippocampal glutamatergic system in memory formation. The simultaneous use of ineffective amounts of scopolamine and MK801 intracerebral (ventral tegmentum area) leads to a decrease in inhibitory avoidance memory.

Effect on the dopaminergic system: Dopamine has been introduced as a potential substrate in synapse plasticity and memory mechanisms. There is pharmacological evidence for the role of dopamine in memory and learning. Recently, it has been observed that dopamine levels transiently increase during processes involved in memory. Additionally, blocking dopamine uptake improves inhibitory avoidance learning and increases acetylcholine release from the hippocampus. However, it is unclear whether stimulation of different dopamine receptors facilitates or impairs memory and learning. Scopolamine injection increases dopamine by inhibiting M2/4 muscarinic autoreceptors. These autoreceptors are located on dopaminergic presynaptic neurons, and their activation reduces the release of dopamine. Therefore, blocking these autoreceptors by scopolamine can increase the release of dopamine. Both D1 and D2 receptors are involved in the process of learning and memory. In general, stimulation of dopamine D1 receptors follows an inverted U-shaped dose-response curve, meaning that both insufficient and excessive amounts of dopamine cause memory impairment. Therefore, one of the mechanisms of scopolamine-induced memory impairment can be an indirect effect on the dopaminergic system.

Effect on the serotonergic system:

Effects of serotonin in the hippocampus were divided into three categories: Effect on cell membrane potential, effect on neuron plasticity, and interaction with acetylcholine. Serotonin plays a complex role in memory and learning. Serotonin receptors (5-HT2A) also play a role in memory function through their effect on calcium transport. This action is similar to dopamine receptors and other G-protein-coupled receptors, which activate phospholipase C, enter calcium into the cell, and activate calcineurin. Activation of 5-HT2A receptors, as well as 5-HT4 receptors by specific agonists of these receptors enhances LTP, which plays a very important role in memory. On the other hand, specific 5-HT3 receptor antagonist improves LTP. The 5-HT6 receptor antagonist can improve memory function. Therefore, different serotonin receptors have different roles in memory function, and the interaction between scopolamine and these receptors needs further study.

Effect on the histaminergic system: The role of histamine and its receptors in some brain processes, such as cognition, has been determined. In addition, histamine plays a role in processes, including the improvement of functional memory after brain damage, learning, memory, and its enhancement. Depletion of histamine content causes side effects in active avoidance and radial maze. Injection of histamine or histidine reverses scopolamine-induced memory impairment. Cholinergic and histaminergic systems in the brain are closely related. It has been shown that histamine increases the secretion of acetylcholine in the hippocampus and postsynaptic H1, and presynaptic H3 receptors play an important role in memory and learning, but whether scopolamine can cause memory impairment through interaction with histamine receptors, not reviewed.

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Not Applicable

Authors' Contribution

Study concept and design: A-K.H and A-R.A.
Acquisition of data: A-R.A.
Analysis and interpretation of data: S.M.
Drafting of the manuscript: A-R.A.

Critical revision of the manuscript for important intellectual content: A.L. and A-R.A.
Statistical analysis: S.M. and A-R.A.
Administrative, technical, and material support: A-R.A.

Ethics

The current research was approved by the Ethics Committee of the University of Falavarjan Branch, Islamic Azad University, Isfahan, Iran.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

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

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