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The effect of apelin-13 on memory of scopolamine-treated rats and accumulation of amyloid-beta plaques in the hippocampus

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Abstract

Background: Neurodegenerative diseases (NDDs) cause progressive neuronal loss, resulting in morbidity and mortality. Research is continued on treatment strategies that can tackle the disease's pathophysiology and cease its progression. Considering the anti-apoptotic and neuroprotective properties of apelin, we hypothesized that apelin-13 could be a therapeutic solution for Alzheimer's disease and similar NDDs. Therefore, we evaluated its effect on scopolamine-treated rats.

Methods: Male rats (n=40) were assigned to 5 groups of 8. No intervention was considered for the control group. The scopolamine group received stereotaxic surgery and was treated with 3 mg/kg scopolamine intraperitoneally. The treatment groups were treated with scopolamine plus intraventricular injection of apelin-13 (1.25, 2.5, and 5 µg) into the right lateral ventricles for 7 days. For evaluating the memory impairment, the passive avoidance reactions of the animals, except the control group, were assessed 24 hours following the last injection. Regarding histological analysis, Congo red staining of the hippocampal sections was done, and immunoblotting was used to determine apoptotic biochemical markers, including caspase 3, cytochrome C, and congophilic amyloid-beta plaques.

Results: Apelin–13 alleviated scopolamine-related passive avoidance memory impairment and reduced the number of congophilic amyloid-beta plaques in the hippocampus (all P<0.001). It attenuated the decrease in the mean levels of hippocampal apoptotic proteins (caspase 3, cytochrome C) in animals treated with scopolamine (all P<0.05).

Conclusion: The neuroprotective effects of apelin-13 suggest its therapeutic effect on neurodegenerative disorders.

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Highlights

What is current knowledge?

Apelin-13 is an endogenous neuropeptide. It plays a role in apoptosis, autophagy, synaptic plasticity, and neuroinflammation

What is new here?

This study suggests that it is an effective and novel treatment for Alzheimer's disease. The effect is proven in molecular and tissue models.

Introduction

Neurodegenerative disorders (NDDs) are a group of diseases characterized by progressive neuronal loss in the brain; the clinical manifestations differ based on the brain region(s) involved and proteins aggregated in neurons and glia (1, 2). Alzheimer's disease (AD) is the most common type of NDD, involving over 50 million patients today. The rate is expected to double by 2050, considering population aging (3). This progressive disease starts with an irreversible decline in episodic memory and in the overall cognitive ability of the patients, which deteriorates and finally results in death (4-8).

Research is continued on the most effective treatment for AD, mainly those tackling the disease pathology to halt its progression (9). An important pathology of AD is related to the accumulation of intracellular neurofibrillary nodules (NFTs) and extracellular amyloid-beta (Aβ) plaques produced by hyper-phosphorylation of the tau protein in normal neurons (10-12). Accumulation of Aβ reduces the number of synapses and synaptic flexibility, resulting in ongoing neuronal damage in the brain and ultimately leading to cell death (13). Another mechanism involved in apoptotic death, expressed and activated in the AD brain, is the caspases, the activation of which is mediated through the mitochondrial release of cytochrome C into the cytosol. Caspase-3 is more likely to be related to neuronal apoptosis regulation in AD (14). Other inflammatory processes have also been suggested to play a role in AD pathogenesis and are used as therapeutic targets (15).

Neuropeptides are signaling molecules used by neurons for information transmission and communicating with each other (16), with the potential to treat human brain disorders (17). Apelin is an endogenous neuropeptide, first isolated from bovine gastric tissue in 1998 (17, 18), found in several human tissues, including the cell body of neurons and nerve cell fibers, such as the hypothalamus, piriform cortex, substantia nigra, striatum, hippocampus, olfactory system, gray matter, amygdala, cerebellum, corpus callosum, pituitary gland, medulla, and the spinal cord. The neuroprotective effect of apelin and its widespread distribution in the central nervous system suggests its potential therapeutic role in neurological disorders (19, 20). Animal studies have confirmed its efficacy on ischemic stroke (21) and Parkinson's disease (22), possibly acting through the inhibition of oxidative stress and neuroinflammation.

Concerning AD, research has suggested the efficacy of apelin on apoptosis, autophagy, synaptic plasticity, neuro-inflammation (23), and direct or indirect prevention of Aβ production by increasing its degradation (16). Apelin-13 is the most abundant member of the apelin family, with high neuroprotective function (24, 25). The role of apelin-13 in the inhibition of Aβ-induced injury and apoptosis in SH–SY5Y cells and increasing cell survival by reducing oxidative stress confirm the critical role of apelin-13 as an anti-AD agent (26). Different mechanisms have been suggested for this role, including its effect on glucocorticoid receptor and FKBP5 (17), brain-derived neurotrophic factor, and tyrosine receptor kinase B in the hippocampus (27). Considering the important role of Aβ and oxidative stress in the pathology of AD and the existing evidence on the possible effect of apelin-13 on AD, there is a need for further studies to confirm its effect on molecular and cognitive functions.

For induction of AD in this animal study, we used scopolamine, which accumulates Aβ in the brain, impairs mitochondrial function, cholinergic function, and antioxidant defense, and increases oxidative stress, apoptosis, and neuro-inflammation (5, 28). The similarity of these pathological changes, induced by scopolamine, to that in AD resulted in its use for inducing AD in experimental models for studying cellular and molecular changes associated with the pathogenesis of AD (5, 18). Considering the evidence stated above on the potential of apelin-13 in the treatment of AD and the need for more investigations to confirm its efficacy, we assessed the effect of apelin-13 on memory impairment, plaque density, and apoptosis in scopolamine-treated rats.

Methods

Chemicals

The used drugs and chemical agents were apelin-13 (Phoenix Pharmaceuticals, Mannheim, Germany), scopolamine hydrobromide (Tocris, Great Britain), primary polyclonal anti caspase-3, Congo red, and primary monoclonal anti-b-actin antibodies, provided by Cell Signaling Technology, USA.

Study populations

Forty male Wistar rats (10 weeks old; 120 to 180 g) were obtained from the Pasteur Institute of Amol and located in clear plastic cages; 8 rats were kept in each cage at room temperature (22 ± 3° C) during the 12-hour light-dark period (7 am to 7 pm) without any noise pollution in the animal lab of Golestan University of Medical Sciences. Animals were fed ad libitum with no restrictions on food and water, except during the experiments. After adaptation to the laboratory environment and following the available references, the following groups (n=8 per group) were considered randomly:

Group 1, control group: no surgery or drug.

Group 2 (sham group), scopolamine group: Following 7 days of recovery from stereotaxic surgery, this group received an intraperitoneal (IP) injection of scopolamine (3 mg/kg), followed by an intraperitoneal injection of 5 µL normal saline on the next day daily for 7 days.

Groups 3, 4, and 5 interventional groups: In these three groups, scopolamine was injected in the same manner as the previous group. On the next day (24 hours later), apelin-13 was injected. The dose of apelin-13 differed among the groups: group 3 received 1.25 µg, group 4 received 2.5 µg, and group 5 received 5 µg apelin-13. Apelin-13, soluble in normal saline, was injected into the right lateral brain ventricles (10 µL Hamilton syringe; needle number 21) at 9 am, once daily for 7 days. The study by Haghparast et al. was used for apelin dose (29). The Ethics Committee of the Neuroscience Research Center of the Golestan University of Medical Sciences approved the protocol of this research.

Passive avoidance learning test

Before the intervention, animals were trained using a passive avoidance device for 1 day, and 16 days later, the memory test was conducted again. Accordingly, after locating the rats in the light compartment, the guillotine door was opened for 5 seconds into the dark box, and the latency was recorded; rats with a latency of >120 seconds were excluded from the study. After half an hour, the door was opened, and animals received a foot shock (50 Hz, 1 mA, 3 seconds) upon entering the dark box. The animals were then transferred to their cages (for 120 seconds). The rats were located in the lightbox again, and the latency was recorded for up to 2 minutes. Successful passive avoidance was considered as no entrance to the dark chamber for at least 120 seconds. On the test day, animals were first located in the lightbox, followed by opening the guillotine door (for 5 seconds) with no foot shock, and the duration of delay was recorded (maximum time: 300 seconds).

Surgery

Animals were anesthetized by IP injections of 2% xylazine and 10% ketamine 48 hours after the experiment to remove their brains. After placing the rats in a stereotaxic device, their hair was shaved and disinfected with 70% alcohol, followed by making a longitudinal incision between the ears and eyes using a scalpel. Connective tissue was isolated, and the device marker was fixed on Bergma. The stereotactic coordinates of the right lateral ventricles were determined on the skull (AP = -0/8 and DV = -4/2; based on the Atlas of Paxinos and Watson) and drilled with a tooth drill. After inserting the guide cannula into the skull, 2 small screws were implanted into the skull (to secure the cannula to the skull bone) and secured using dental acrylic. After drying and hardening the acrylic teeth, the rats were removed from the apparatus, transferred to a warm place, and maintained in separate cages until they regained consciousness (29).

Histology

After brain removal, the brain tissues were fixed in phosphate buffer saline, including a 4% paraformaldehyde solution, for 1 week. An automated tissue processor (Green Vision, Urmia, Iran) was used for the histological processing, and the brains were embedded in paraffin blocks. A rotating microtome (Pooyan MK 1110, Iran) cut the brain sagittally (6-µm-thick) and formed the hippocampus (lateral, 0.90 to 4.32 mm).

After deparaffinization and hydration with xylene and ethanol, 6-µm-thick brain sections were stained for 5 minutes with 1% Congo red (Sigma, MO, USA), washed with distilled water twice, and dehydrated in 96% and 100% ethanol. After cleaning in xylene, they were covered with Entellan. Images were taken from samples using a Tokyo Olympus BX51 microscope with a DP 72 digital camera. We only examined right-hemispheric hippocampal neurons. First, the hippocampus was identified using a 4× microscope lens, and 40 areas were imaged using a magnifying glass. After images, the hippocampal CA1, CA2, CA3, CA4, and dentate gyrus (DG) areas were first graded by Image J software; the same software was used for counting the 30 000-µm area for each hippocampal area (29).

Canola approval

Animals were randomly selected to confirm the appropriateness of cannula placement in the lateral ventricle. In addition, the cannula was injected with 0.5 µL methylene blue. Animals were exterminated 60 minutes later, and after brain removal, they were placed in a formaldehyde solution (10%). The next day, a microtome (Leitz, Germany) cut serial 3-µm incisions, and the cannula tip was placed in the lateral ventricle under microscopic control.

Western blot analysis for cytochrome C and cleaved caspase–3

Carbon dioxide-induced anesthesia was administered. The rats' brains were isolated immediately, washed using cold normal saline, and kept on ice-cold glass plates. The right striatum was promptly removed, and its tissue homogenization was performed in ice-cold buffer including EDTA (1mM), 10mM Tris–HCl (pH 7.4), 0.1% SDS, 0.1% sodium–deoxycholate, 1% nonyl phenoxypolyethoxylethanol–40, and protease inhibitors, including 1mM phenyl methyl sulfonyl fluoride, 2.5mg/mL leupeptin, and 10mg/mL aprotinin, and 1mM sodium orthovanadate. After centrifuging the homogenate at 14 000g/15 min/4 °C, the supernatant was collected as the whole tissue sample, and the total protein level was calculated by the Bradford approach (Bio-Rad Laboratories, Germany). Electrophoresis was performed using similar levels of protein (40 mg) on 12% sodium dodecylsulfate–polyacrylamide gel electrophoresis (SDS-PAGE) transmitting into polyvinylidene difluoride (PVDF) membrane (Roche, Germany). Following 2 h of blocking at room temperature by 5% non-fat dried milk in Tris-buffered saline 0.1% Tween 20 (TBST), the membranes were probed via initial polyclonal cytochrome C antibody (sc–376861, Santa Cruz Biotechnology) and monoclonal anti-caspase-3 antibodies (Cell Signaling Technology, USA) (1:1000) for 1 night at 4 °C. After being washed 3 times by TBST (in 5 min), the blots were incubated for 60 min at room temperature using diluted horse-radish peroxidase-conjugated secondary antibodies (1:10000, Santa Cruz Biotechnology). We applied a pre-stained protein ladder (SM7012, Cinagen Co, Iran) to monitor protein purification and estimate the molecular weight and united intensity of the blotting bands. An ECL system was used to identify the antibody-antigen complex, subjected to Lumi–Film chemiluminescent detection film (Roche, Germany). To evaluate the blotting bands' intensity, we used LabWorks Software (UVP, UK). Beta-actin (1:10 000) was applied as a loading control, and the expression scores were expressed as studied proteins/b-actin proportion per animal (29).

Data analysis

SPSS v. 21.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Mean and standard deviation (SD) were applied to describe the numerical variables. One-way analysis of variance was employed to compare the means between groups. Further significant differences were assessed using the Student-Newman-Keuls (S-N-K) test. A P-value <0.05 was regarded as significant.

Results

A. Behavioral Results

Testing the passive avoidance memory showed that scopolamine significantly reduced mean passive avoidance latency (sec), and apelin-13 increased the mean values. A comparison of the therapeutic groups with the scopolamine group showed significant differences in 1.25 and 2.5 µg doses of apelin-13 (Figure 1).

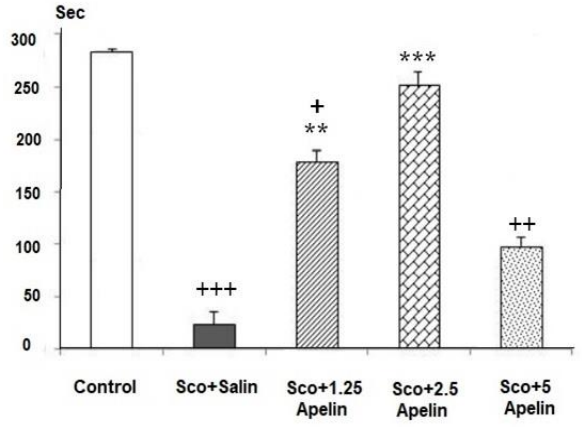

Figure 1. Effect of apelin-13 on mean passive avoidance latency in the studied groups. #: (47).
The groups included control, scopolamine, scopolamine + 1.25 µg/kg/day apelin-13, scopolamine + 2.5 µg/kg/day apelin-13, and scopolamine + 5 µg/kg/day apelin–13.
For intergroup comparisons: ^{+}P <0.05, ^{++}P <0.01, and ^{+++}P <0.001 vs. the controls $^{**}P$ <0.01, and $^{***}P \leq 0.001$ vs. the scopolamine-treated group.

B. Density of congophilic amyloid-beta plaque in the hippocampus region

The number of Aβ plaques in the CA3 region of the hippocampus decreased in groups 3 and 5 (which received 2.5 and 5 µg apelin-13, respectively) compared to the sham group (group 2, P <0.001; Figure 2). The lowest amount of Aβ plaque in the CA3 region was found in group 5. Figure 2 illustrates the images obtained from the microscopic evaluation of hippocampal areas, stained by Congo red in each group.

C. Cytochrome C, assessed by Western blotting

The results of evaluating cytochrome C showed higher mean values in the scopolamine group (group 2) than in the control group (group 1; P<0.001). Comparing the therapeutic groups with the sham group showed a lower mean value of cytochrome C in groups 3 and 4 (which received 1.25 and 2.5 µg/kg/day apelin-13, respectively) compared to the scopolamine group. In group 5 (which

received µg/kg/day apelin-13), the mean values of cytochrome C were not different from the scopolamine group but differed from the control group (P<0.001; Figure 3).

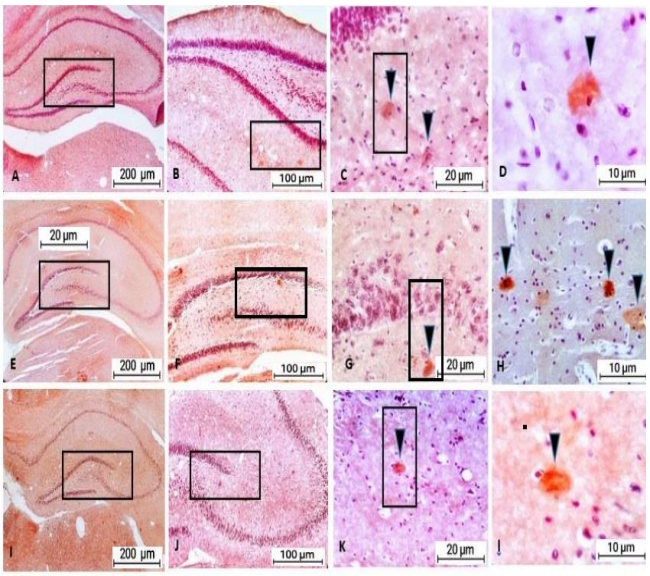

Figure 2. Congo red staining in right hippocampal areas in the five study groups: control group (A, B, C, and D), scopolamine group (E, F, G, and H), and scopolamine + apelin–13 group (I, J, K, and L); Red arrows show live plaques in the hippocampus.

D. Caspase-3, assessed by Western blotting

The results of evaluating caspase-3 showed higher mean values in group 2 (scopolamine group) than in the control group (P<0.001). Comparing the values in therapeutic groups with the sham group showed lower mean values in groups 3 and 4 (1.25 and 2.5 µg/kg/day apelin-13, respectively) compared to the scopolamine group. In group 5 (which received 5 µg/kg/day apelin-13), mean values of caspase-3 were not different from the scopolamine group but differed from the control group (P<0.001; Figure 3).

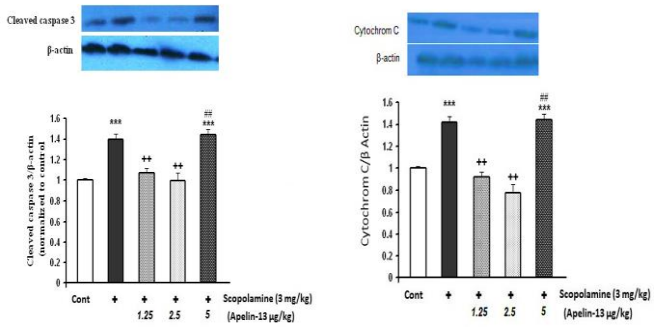

Figure 3. The effect of apelin-13 on scopolamine-induced caspase-3 and cytochrome C. Each value indicates the mean band density ratio in each group. Beta-actin was an internal control for loading. ***P <0.001 vs. the controls, ++P <0.01 vs. the scopolamine group, ##P value vs. 1.25 µg/kg/day apelin-13

Discussion

We investigated the effect of apelin-13 neuropeptide on several parameters; the first and most important parameter was the density of Aβ plaques in the hippocampus (CA1, CA2, CA3, CA4, and DG areas). The results showed the highest effect in the highest dose (5 µg). These results confirmed our hypothesis, implying that apelin had neuroprotective effects against AD by reducing the density of the Aβ plaques accumulated in the hippocampus. Considering the previous evidence, Aβ is primarily responsible for cognitive impairment and neurological death in AD, and Aβ antagonists can treat AD by reducing Aβ production by inhibiting β and γ–secretase enzymes and eliminating cerebral Aβ plaques (30). This mechanism may be the same mechanism of action for the effect of apelin-13 on Aβ concentration, which suggests it is a promising candidate for AD treatment. Other mechanisms have also been introduced for the direct or indirect effect of apelin on inhibiting the production of Aβ (31), including reducing the amount of APP and decreasing β–secretase activity. It has been suggested that by increasing the level of ATP-binding cassette subfamily A1 (ABCA1) and the activity of neutral endopeptidase, it degrades and reduces Aβ (16, 32). Luo et al. (2019) investigated the impact of apelin on various physiological processes of AD and found that apelin plays an essential role in suppressing inflammatory responses, inhibiting oxidative stress, reducing calcium (Ca^{2+}) signaling, suppressing apoptosis, and inducing autophagy. Thus, apelin was presented as a new strategy for managing neurological diseases (33).

In a previous study, our team showed the protective effect of apelin-13 on human neuroblastoma cells (SH–SY5Y) (34). Chen et al. reported the neuroprotective effect of apelin-13 against rotenone–related neurotoxicity through activation of AMPK/mTOR/ULK–1 medicated autophagy (35). Others have also shown the effect of apelin-13 on oxidative stress-induced apoptosis (36). All these studies are consistent with the findings of the present study and imply that apelin-13 can be considered a practical therapeutic agent in AD.

The second important parameter evaluated in the present study was memory impairment, evaluated by passive avoidance latency. The results showed improved memory in therapeutic groups after the substantial decrease in scopolamine. Other studies have shown the positive effect of apelin-13 on memory as well. In 2019, Yavari et al. examined the effect of apelin-13 on Aβ-induced memory impairment and autophagy and apoptotic processes in the hippocampus. They found that apelin-13 significantly protected against the destructive effects of Aβ. Apelin-13 also significantly protects against the destructive effects of Aβ on memory and improves Aβ–induced functional disorders and spatial memory by inhibiting autophagy and suppressing apoptosis (31). These results, in line with our study, showed the favorable effect of apelin-13 on memory impairment, implying that this agent is not only effective in the molecular phase but also influences the clinical symptoms. Removal or reduction of amyloid plaques from the hippocampus of rats with AD is possibly the underlying mechanism of increased memory (37).

In order to evaluate how apelin-13 can influence or treat AD, we evaluated another mechanism, which has been suggested to play a role in AD in addition to Aβ plaque formation. Considering the significance of oxidative stress and apoptosis in the pathogenesis of NDDs and AD, we evaluated caspase-3 and cytochrome C values. The results showed that the increased mean values in the scopolamine group were attenuated in groups receiving 1.25 and 2.5 µg/kg/day apelin-13. In the previous study from our team, we demonstrated the effect of apelin-13 on the inhibition of caspase-3 and cytochrome C increase (34). A similar effect was observed in hair cells derived from bone marrow; as suggested, protein expression of caspase-3 and Bax/Bcl-2 were significantly lower in the group pretreated with apelin-13 (36). Activation of the caspase cascade is important for apoptosis, initiated by caspases 2, 8, and 9, and followed by executive caspases, such as 3, 7, and 14 (38); therefore, inhibition of caspase-3 can be an important step for reducing or inhibiting apoptosis, the main mechanism of cell death in AD. Zang et al. also showed that apelin-13 decreased cytochrome C release and inactivated caspase-3 in cultured mouse cortical neurons (39), which confirms the results of the present study. Decreased levels of cleaved caspase-3 and caspase-9, induced by apelin-13, were also detected in the SHSY5Y cell line in the rat vascular dementia model (40). Different pathways have been suggested for the mechanism of action for this effect, including inhibiting the activation of ATF6/CAAT enhancer binding proteins homologous protein-CHOP pathway (41) and glucagon-like peptide-1 receptor/PI3K/AKT signaling pathway (42). The effect of apelin-13 on cytochrome C efflux and apoptosis has also been suggested in regulating mitochondrial dysfunction for the prevention of lung injury (43). Further studies are required to determine how apelin-13 decreases caspase-3 and cytochrome c levels.

In this study, in addition to the effect of apelin-13, we also showed the effect of scopolamine in rats by evaluating the parameters in the sham group; as shown, intraperitoneal injection of 3 mg/kg scopolamine can cause increased amyloid plaques in CA1, CA2, CA3, CA4, and DG regions in rat hippocampus, and staining with Congo red confirmed the accumulation of Aβ plaques in the hippocampal tissue. These findings suggest that scopolamine injection causes similar changes as AD. Previous evidence has also suggested that scopolamine is an appropriate model of AD (44), resulting in atrophy and degeneration of the brain's nerves, mitochondrial dysfunction, increased apoptosis of hippocampal neurons, neuroinflammation, and oxidative disorders in rats through Aβ accumulation in the brain (5). Therefore, scopolamine injection has been used in several studies for inducing AD in animals (45, 46). Our results also showed the successful induction of the AD model in rats by scopolamine injection; this finding confirms its use in further studies for the rat AD model.

An important strength of the present study was the simultaneous evaluation of cellular and behavioral (memory function) tests in one study, which can provide strong evidence for the effect of apelin-13 on AD. However, we only evaluated 3 cellular mechanisms in this study, namely Aβ accumulation, caspase-3, and cytochrome C, and performed only 1 behavioral test, while other mechanisms may also be involved, which were not evaluated in this study.

Conclusion

In this study, with the help of scopolamine, we successfully induced an AD model in rats and showed that apelin-13 alone could significantly reduce the scopolamine-induced cell damage by preventing the accumulation of Aβ plaques on the hippocampus neurons and reducing the destructive effects of Aβ on neurons. We also showed that apelin-13 could reduce the levels of caspase-3 and cytochrome c, important agents in the apoptosis cascade. The favorable effect of apelin-13 on AD was also confirmed by improving the memory impairment induced by scopolamine in the rats. Therefore, apelin-13 should be considered in future research on novel treatments for AD to define whether this treatment can improve memory loss and other AD symptoms in humans.

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Ethical statement

The protocol of this research was confirmed by the Ethics Committee of Golestan University of Medical Sciences Neuroscience Research Center IR.GOUMS.REC.1399.156 .NA (This study was not conducted on humans).

Conflicts of interest

The authors have no conflict of interest

Author contributions

L. Elyasi was involved in idea formation and writing the manuscript. M. Jahanshahi was involved in statistical analysis and writing the manuscript. Behnaz Bazrafshan, Maryam Azhir, and Sara Gazme performed the study on rats, collected the data, and were involved in preparing the materials. All the authors confirmed the final version of the manuscript.

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