Molecular Neurobiology
https://doi.org/10.1007/s12035-024-04388-x

RESEARCH

Selegiline Improves Cognitive Impairment in the Rat Model of Alzheimer's Disease

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Received: 21 November 2023 / Accepted: 19 July 2024

Abstract

Alzheimer's disease (AD) is a progressive neurological disorder characterized by cognitive decline. This study was undertaken to evaluate the effects of selegiline (SEL) against AD-induced cognitive deficits and explore the possible involved mechanisms. AD was induced by unilateral intracerebroventricular (U-ICV) injection of 5 µg of amyloid beta$_{1\text{-}42}$ (A$\beta_{1\text{-}42}$), and oral administration of SEL (0.5 mg/kg/day) was performed for 30 consecutive days. Aβ injection resulted in spatial cognitive decline, as demonstrated by a decrease in the time spent in the target zone on the probe day ($P<0.01$) in the Barnes maze test (BMT). This spatial cognitive decline was associated with disrupted synaptic plasticity, as indicated by reductions in both components of hippocampal long-term potentiation (LTP), namely population spike amplitude ($P<0.001$) and field excitatory postsynaptic potential ($P<0.001$). On the other hand, the injection of Aβ resulted in oxidative stress by decreasing total thiol group (TTG) content and increasing malondialdehyde (MDA) levels in the rat plasma ($P<0.001$). Additionally, the number of healthy cells in the hippocampal dentate gyrus (DG) and CA1 regions was reduced in AD rats ($P<0.001$). However, oral administration of SEL improved spatial cognitive decline in the Aβ-induced AD rats. The results suggest that improvement of neuroplasticity deficiency, regulation of oxidant/antioxidant status, and suppression of neuronal loss by SEL may be the mechanisms underlying its beneficial effect against AD-related spatial cognitive impairment.

Keywords Alzheimer's disease · Selegiline · Spatial memory · Long-term potentiation · Oxidative stress

Introduction

Alzheimer's disease (AD) is a progressive neurological disorder and the main cause of cognitive decline, affecting mental capacity and cognitive function [1]. Several risk factors such as increasing age, genetic factors, head injuries, and environmental factors are implicated in the development of this multifactorial disease [2]. The pathology of AD is studied to understand different mechanisms, such as abnormal metabolism of tau protein, amyloid beta (Aβ), inflammatory response, cholinergic dysfunction, and oxidative stress [3]. Aβ plays a major role in neuronal toxicity and impairment of neuronal function, so the accumulation of Aβ plaques in the hippocampus, amygdala, and cerebral cortex can lead to axonal damage, dendritic loss, synaptic loss, and cognitive impairments [4]. Oxidative stress and Aβ are interconnected and positively affect each other's increase. The brain's vulnerability to oxidative stress, caused by decreased antioxidants or accumulation of free radicals within cells, is considered a critical detrimental factor in AD. AD begins years before its symptoms appear, and antioxidant therapy can be an important therapeutic target to combat this disease [5]. However, to date, there is no definitive treatment that completely halts the progression of AD. Therefore, finding effective treatments for AD can be highly valuable.

It has been shown that monoamine oxidase B (MAO-B) expression increases in AD brains' cortex and hippocampus compared to healthy brains [6]. Furthermore, there is a significantly more than three-fold increase in active MAO-B in reactive astrocytes surrounding Aβ deposits [7]. This excessive expression of MAO-B in astrocytes is believed

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Published online: 13 August 2024

to contribute to the improper breakdown of monoamine neurotransmitters (dopamine, norepinephrine, epinephrine, and serotonin) and the heightened production of free radicals and hydrogen peroxide (H_2O_2), potentially promoting the observed neurodegenerative processes in AD [8]. This phenomenon appears to be an early occurrence in AD that persists throughout the progression of the disease [9]. These findings suggest that the inhibition of MAO-B through drugs may offer a new strategy to alleviate the pathological symptoms of AD [10].

Selegiline (SEL), a selective and irreversible inhibitor MAO-B, is clinically used to slow the progression of Parkinson's disease (PD) [11]. SEL exhibits a wide spectrum of biological properties, including anti-inflammatory [12], anti-apoptotic [13, 14], neurotrophic [15, 16], and cognitive-ameliorating effects [17, 18]. Previous studies have demonstrated SEL's ability to scavenge reactive oxygen species (ROS) and suppress lipid peroxidation in various neurodegenerative diseases and insult models, including PD [19], cerebral ischemia [20], scopolamine-induced memory deficits [21], and 3-nitropropionic acid (3-NP)-induced neurotoxicity [22]. Additionally, SEL has shown neuroprotective properties in conditions such as traumatic brain injury (TBI) [23], cerebral ischemia [20, 24], schizophrenia [25], PD [26], and major depressive disorder [27]. Given SEL's capability to increase levels of monoamine neurotransmitters, particularly dopamine [28], it offers a potential avenue for improving cognitive deficits associated with AD. Preclinical and clinical trials have been conducted to evaluate SEL's efficacy in treating cognitive deficits associated with AD [29–33]. However, the underlying mechanisms involved in SEL's therapeutic effects on AD-associated cognitive deficits remain poorly understood.

Therefore, this study aimed to investigate the effects of chronic oral administration of SEL on spatial cognitive ability in an $A\beta_{1\text{-}42}$-infused AD rat model. Additionally, this study aimed to identify specific underlying mechanisms, including hippocampal synaptic plasticity and oxidative stress.

Materials and Methods

Animals and Experimental Design

Forty adult male Wistar rats were obtained from the animal house of Hamedan University of Medical Sciences (Hamedan, Iran), with a weight range of 210 to 230 g. The rats were housed in an animal room with a controlled temperature of 22 ± 2 ℃, relative humidity of 60 ± 5%, and a 12-h light–dark cycle, with free access to food (47% carbohydrate, 5% fat, 23% protein, 5% fiber, 20% water, vitamins, and minerals) and water. Animal care and experimental procedures were conducted in accordance with NIH guidelines and approved by the ethics committee of Bu-Ali Sina University–Hamedan (ethical code IR.BASU.REC.1400.001). After a 7-day adaptation, the rats were randomly divided into five groups of eight as follows:

I. Control group: Rats received 5 ml/kg/day of 0.9% normal saline via oral gavage (P.O.) for 30 days.
II. PBS group: Rats received a stereotaxic unilateral intracerebroventricular (U-ICV) injection of phosphate-buffered saline (PBS; 5 µL/rat) plus normal saline (5 ml/kg/day; P.O. for 30 days).
III. SEL group: Rats received SEL (0.5 mg/kg/day; P.O. for 30 days).
IV. AD group: Rats received a stereotaxic U-ICV injection of 5 µL of $A\beta_{1\text{-}42}$ (1 µg/µL) plus normal saline (5 ml/kg/day; P.O. for 30 days).
V. AD + SEL (AS) group: Rats received SEL (0.5 mg/kg/day; P.O. for 30 days) after a stereotaxic U-ICV injection of 5 µL of $A\beta_{1\text{-}42}$ (1 µg/µL).

A solution of SEL was prepared immediately before use and administered once daily for 30 consecutive days via oral gavage. The dose of SEL used in this study was chosen based on available literature [34–39]. Numerous studies have reported that administration of SEL at the dose of 0.5 mg/kg in animal models has beneficial effects on behavioral, electrophysiological, and neurochemical features [34–39]. Figure 1 shows the experimental timeline. Following 1 week of adaptation to the laboratory environment, Aβ solution injection was performed. Subsequently, the rats had 7 days of recovery. The Barnes maze test (BMT) was assessed from the 31st 34th ($n = 8$). Hippocampal long-term potentiation (LTP) was evaluated on the 35th day ($n = 8$). The biochemical assessments ($n = 8$) and histological analysis ($n = 4$) were also examined on the same day.

AD Induction

Based on previous studies [40–43], a 5-µL solution of Aβ (1 mg/mL) was administered to induce AD in rats. Therefore, Aβ $peptide_{1\text{-}42}$ rat (product No/SKU SCP0038-1MG, Sigma–Aldrich, USA) was dissolved in PBS solution. Before U-ICV injection, the Aβ solution was incubated at 37 °C for 4 days. Amyloid fibrils are produced during this process, which are neurotoxic [41, 44].

For AD induction, each rat was anesthetized by intraperitoneally (I.P.) injection of a mixture of ketamine (100 mg/kg) and xylazine (10 mg/ kg). Stereotaxic (Dual Lab Standard Stereotaxic apparatus; Stoelting Co., Wood Dale, IL, USA) surgery was performed according to Paxinos and Watson's rat brain atlas [45]. The head was shaved, and a midline sagittal incision was made in the scalp. A tiny hole was drilled carefully up to the level of the dura mater in

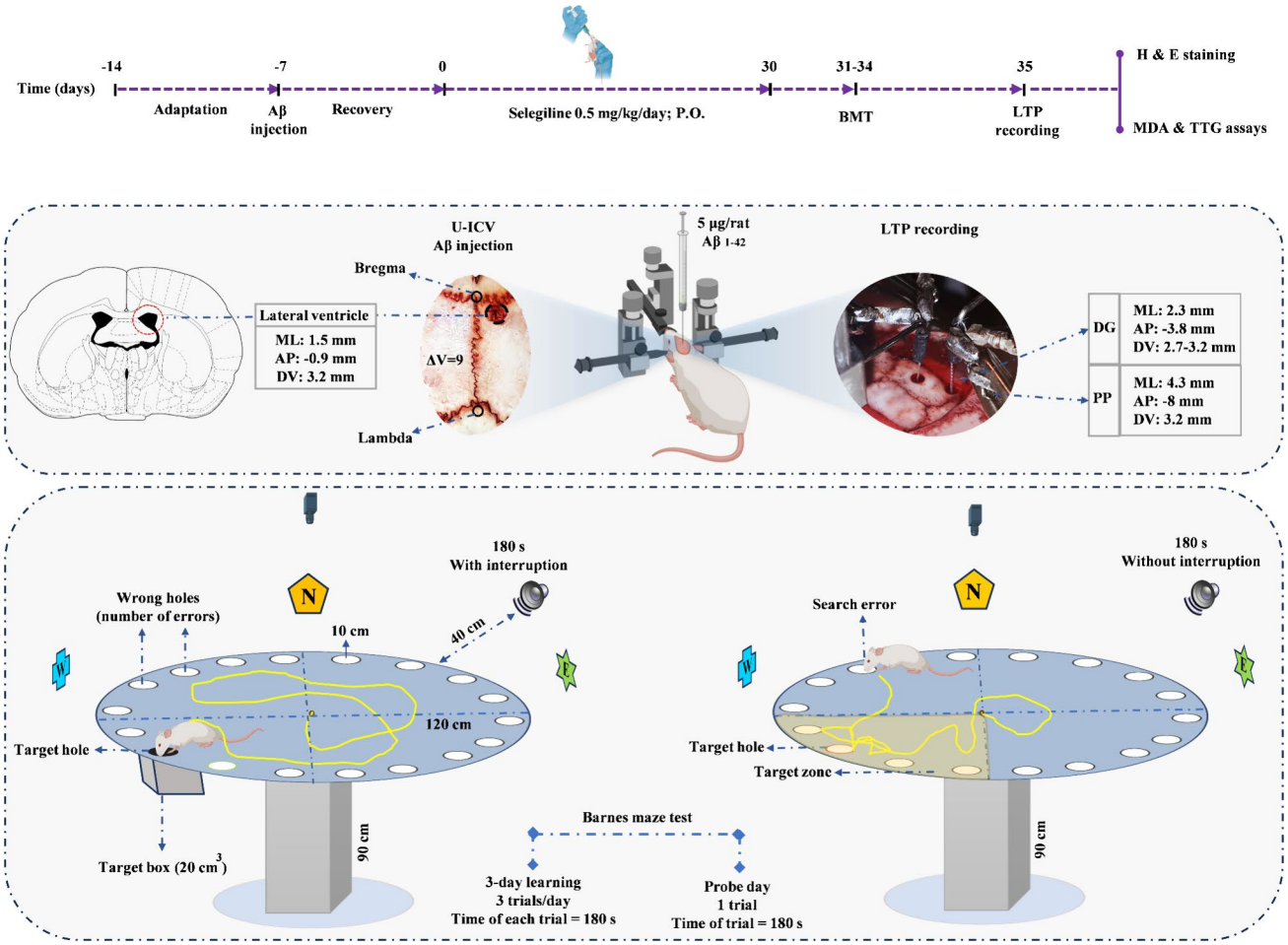

Fig. 1 The rats underwent a unilateral intracerebroventricular (U-ICV) injection of a 5-μL solution of $A\beta_{1-42}$ (1 mg/mL). Selegiline was administered at a dose of 0.5 mg/kg/day; P.O. for 30 days. Subsequently, spatial memory testing and LTP recording were performed. At the end of the experiment, plasma biomarkers (MDA and TTG) were measured, and hematoxylin and eosin staining were performed on the hippocampal tissue

the skull over the ventricular region (coordinates relative to bregma: medial–lateral (M/L), 1.5 mm and anterior–posterior (A/P), − 0.9 mm). Hamilton syringe needle was slowly directed down to beneath the surface of the cortex for the U-ICV injections, into the right lateral ventricle (coordinates relative to the skull: dorsal–ventral (D/V), 3.2 mm) [45]. A 5-μL of Aβ solution was administered at a 1 μL/min rate. The PBS group received 5 μL of PBS (10 mM), the same volume as the Aβ injection (Fig. 1).

Barnes Maze Test (BMT)

The BMT provides a means to measure spatial learning and memory, similar to the Morris water maze (MWM). However, the BMT imposes less stress on the rats than the MWM, which involves swimming in water [46]. The BMT is positioned 90 cm above the ground. It consists of a gray circular platform with a diameter of 120 cm, divided into four hypothetical equal zones (northeast, northwest, southeast, and southwest). There are 18 holes with a diameter of 10 cm around the circular platform. At the bottom of one of the holes, a black box (20 cm^3) is placed and considered the target hole. In the testing room, various spatial cues are visible in four directions for the animal on the platform (Fig. 1). This test aims to measure the ability to learn and remember the location of the target hole and box using the installed cues on the walls. The rat is initially placed in the center of the platform so that the movement of all rats is recorded equally from the center of the platform. An 80-dB noise acts as an escape stimulus for the animal, emitted by a hidden audio device 40 cm away from the circular platform. This loud sound stops by finding the target hole and the rat entering the target box to stimulate the animal to enter the box. The bell rings again if the rat moves away from the target hole. After the rat spends 20 s in the escape box, it is taken out of the BMT. This learning phase of the test

was repeated for 3 consecutive days as learning days (3 trials per day, with a 60-min interval between each repetition, each trial for 180 s). In these stages, the learning process of the animal was measured based on the time spent (escape latency) and distance traveled in the maze until entering the target box, as well as the number of search errors (checking non-target holes). On the fourth day (Probe), the target box was removed and the activity of the rat was recorded for 180 s without interrupting the sound. The time spent in the target zone and the number of search errors were recorded. All sessions were recorded with a camera and video tracking software.

Long-Term Potentiation (LTP)

The urethane solution (1.5 g/kg, I.P.) was injected for deep anesthesia and then the rat was placed in the stereotaxic apparatus. The locations of the dentate gyrus (DG coordinates were AP, – 3.8 mm and ML, 2.3 mm relative to bregma; DV, 2.7 to 3.2 mm relative to the surface of the skull) and perforant pathway (PP coordinates were AP, – 8 mm and ML, 4.3 mm relative to bregma; DV, 3.2 mm relative to the surface of the skull) were determined using the Paxinos atlas, and two holes were drilled in the designated points on the skull (Fig. 1). The stimulating and recording electrodes (stainless steel with Teflon cover, 125 µm bare diameter, 175 µm coated diameter, A.M. Systems Inc., USA) were moved gently to the PP and DG, respectively (Fig. 2a). Single 0.1 ms biphasic square wave pulses at the frequency of 0.1 Hz were used for stimulation (eProbe software protocol in baseline stimulation: delay, 20,000 µs; pulse duration, 200 µs; pulse cycle, 100 µs, train: one; trial numbers, 10; trial period, 10 s). The baseline stimulation intensity for each rat was calculated based on the input–output (I/O) curve. This curve was plotted by recording the amplitude of population spikes (PS) at varying intensities, and 40% of the maximum response was considered as the baseline stimulation intensity (Fig. 2c). When the response was stable in a 10–20 min control period, LTP was induced using a high-frequency stimulation (HFS) protocol of 400 Hz (eProbe software protocol in HFS: delay, 0 µs; pulse duration, 200 µs; pulse cycle, 2500 µs, train, 20; trial numbers, 10; trial period, 10 s).

Using the eLab system (ScienceBeam, Iran) and related computer software (eProbe), the PS amplitude and the slope of field excitatory postsynaptic potentials (fEPSP) were recorded at 5, 30, and 60 min after HFS in the granular cells layer of hippocampal DG following stimulation of the PP.

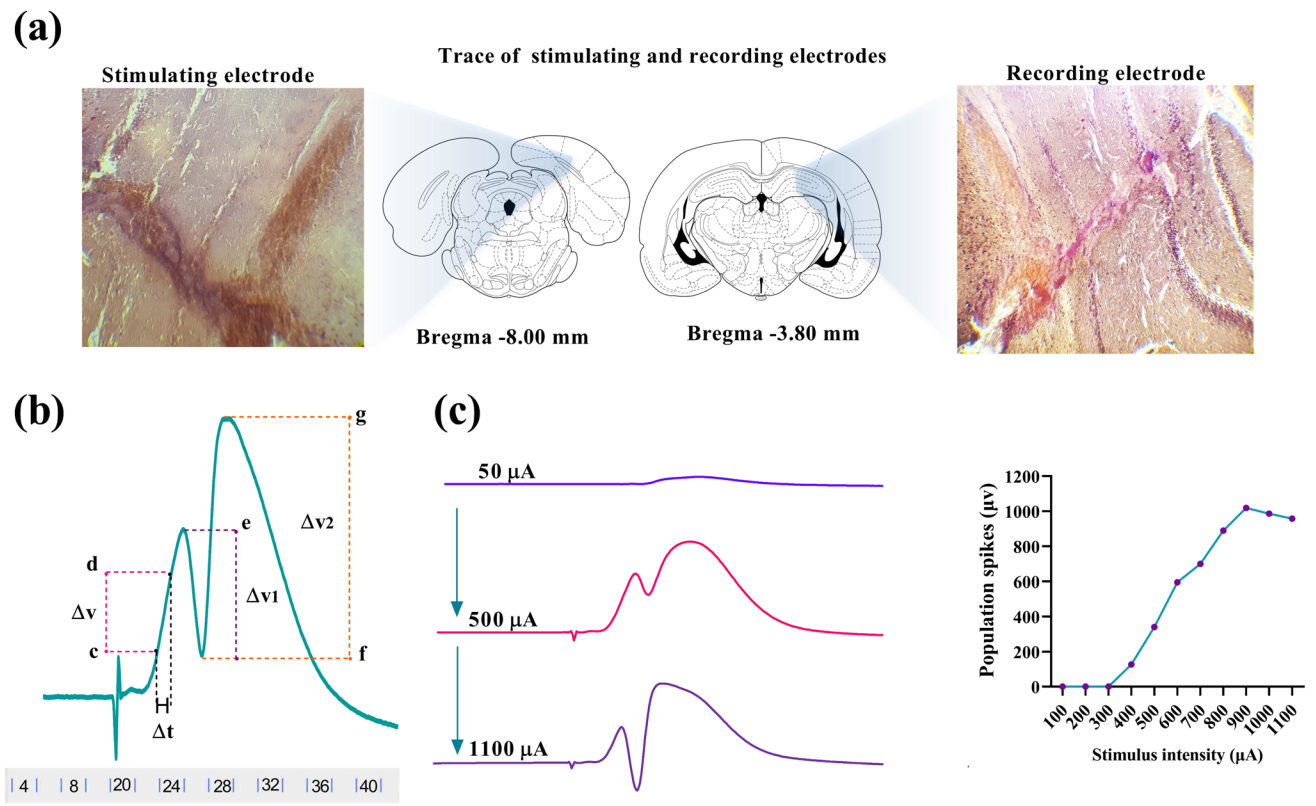

Fig. 2 The positions and traces of stimulating and recording electrodes on the DG and PP are represented in the transverse section of the hippocampus (**a**). Measurement of evoked potentials (**b**). Sample of an I/O curve of PS amplitude in hippocampal DG following PP stimulation (**c**)

Changes in PS amplitude and fEPSP slope were calculated during electrophysiological recordings, according to Eqs. 1 and 2, respectively (Fig. 2b):

$$\text{PS amplitude} = \frac{\triangle V1 + \triangle V2}{2} \quad (1)$$

$$\text{fEPSP } slope = \frac{\triangle V}{\triangle T} \quad (2)$$

where ΔV_1 = The potential difference between two points e, as the peak of the first positive wave, and f, as the peak of the first negative deflection; ΔV_2 = The potential difference between two points g, as the peak of the second positive wave and f as the peak of the first negative deflection; ΔT = Time difference between two points c and d; ΔV = The potential difference between two points c and d, that were between 20 and 80% of the first positive wave.

The values of the fEPSP slope and the PS amplitude at 5, 30, and 60 min were normalized relative to their baselines to measure the LTP magnitude (Eq. 3). Significant increase ($P < 0.05$) in PS amplitude and fEPSP slope (% change) was considered as a successful induction of LTP [41, 47, 48].

$$\text{LTP} = \frac{\text{PS amplitude or fEPSP slope after HFS} \times 100}{\text{PS amplitude or fEPSP slope at baseline}} \quad (3)$$

Biochemical Assay

Blood samples were collected from the hepatic portal vein. Each sample was centrifuged at a speed of 3500 rpm for 20 min, and then the clear plasma was divided into 100-µl aliquots and stored at − 80 ℃ until use. Malondialdehyde (MDA) and total thiol group (TTG) measurement kits were used according to the manufacturer's protocols to calculate oxidative and antioxidant biomarkers levels in rat plasma.

Histology Analysis

After blood collection, four rats from each group were perfused with 0.9% normal saline and 10% formalin solution. Brains were fixed in a 10% formalin solution for 72 h. A 21-h protocol was performed in a tissue processor, and the brains were embedded in paraffin. Sections with a thickness of 5 µm were cut. After deparaffinization and rehydration, the sections were washed in distilled water. Hematoxylin–eosin staining was performed according to standard methods: staining with hematoxylin (8 min), rinsing in tap water, placing in 1% HCL and lithium carbonate (each for 30 s), staining with eosin (2 min), rinsing in tap water, rinsing in graded alcohol, and finally clearing in xylene. The number of healthy pyramidal cells in the hippocampus's dentate gyrus (DG) and CA1 regions was counted.

Statistical Analysis

Data were analyzed and plotted using GraphPad Prism software, version 9 (GraphPad Software, San Diego, CA, USA). Normality of data was assessed using the Shapiro–Wilk test ($P > 0.05$). Analysis of variance (ANOVA) was performed, and if significant, post hoc analysis (based on equal variance of groups in Bartlett's test and number of evaluated groups) was used. Data of BMT (distance moved, escape latency, and number of errors in learning days) and LTP (fEPSP slopes and PS amplitudes) related to the treatment (normal saline or SEL) and exposure (Aβ or non-Aβ) were compared and analyzed by Repeated-measures two-way ANOVA (two-way RM ANOVA) followed by Tukey's post hoc test. The results of the mean percentage of potentiation between groups in LTP, time spent in the target zone on probe day of BMT, oxidative stress, and neuron counting data were compared using one-way ANOVA followed by Tukey's or Bonferroni's post hoc test. In all statistical analyses, $P < 0.05$ was considered significant, and the results were presented as mean ± standard deviation (mean ± SD).

Results

Body Weight

There was no significant difference in initial weight among the study groups ($F_{(4, 35)} = 1.005$, $P = 0.41$). Additionally, no significant difference in final weight was observed at the end of the study ($F_{(4, 35)} = 2.12$; $P = 0.09$, Fig. 3).

The Effects of SEL on the BMT in AD Rats

A sample of recorded activities in the BMT is shown in Fig. 4a. Two-way RM ANOVA showed a significant difference in distance moved to reach the target box over the 3 days of training in terms of the time ($F_{(2, 21)} = 157.0$, $P < 0.001$), treatment ($F_{(4, 84)} = 9.71$, $P < 0.001$), and time × treatment interaction effect ($F_{(8, 84)} = 4.48$, $P < 0.001$). Subsequent Tukey's post hoc test revealed a significant increase in the AD group compared to the control group on the second ($P < 0.01$) and third ($P < 0.001$) days. Oral administration of SEL resulted in a significant decrease in the AS group compared to the AD group on the second ($P < 0.05$) and third ($P < 0.01$) days of learning (Fig. 4b). However, the injection of PBS in the rats of the PBS group and administration of selegiline in the SEL group had no significant effect on the distance moved to reach the target box over the 3 days of training compared to the control group ($P > 0.05$ for each comparison).

Similarly, two-way RM ANOVA showed a significant difference in the time taken to reach the target box over

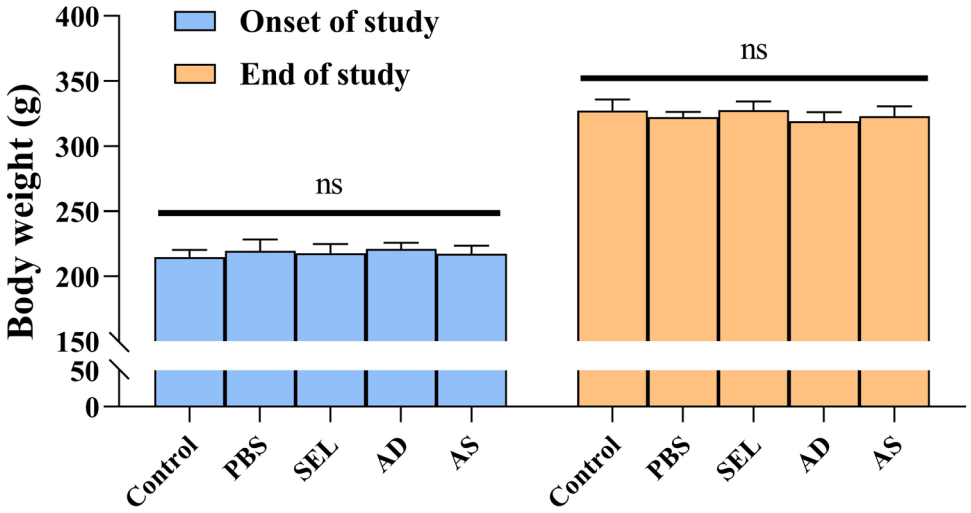

Fig. 3 Effects of selegiline on body weights of AD rats. Data is presented as means ± SD of 8 animals per group (one-way ANOVA). ns, no significance

the 3 days of training in terms of the time ($F_{(2, 21)} = 134.7$, $P < 0.001$) and treatment ($F_{(4, 84)} = 10.37$, $P < 0.001$). However, there was no significant time × treatment interaction effect ($F_{(8, 84)} = 0.939$, $P = 0.488$). Tukey's post hoc test revealed a significant increase in the AD group compared to the control group on the second ($P < 0.05$) and third ($P < 0.01$) days. Oral administration of SEL resulted in a significant decrease in the AS group compared to the AD group on the second ($P < 0.05$) and third ($P < 0.05$) days of learning (Fig. 4c). However, the injection of PBS in the rats of the PBS group and administration of selegiline in the SEL group had no significant effect on the time taken to reach the target box over the 3 days of training compared to the control group ($P > 0.05$ for each comparison).

Additionally, two-way RM ANOVA showed a significant difference in the number of errors in searching for the hidden box over the 3 days of training in terms of the time ($F_{(2, 21)} = 453.5$, $P < 0.001$) and treatment ($F_{(4, 84)} = 8.30$, $P < 0.001$). However, there was no significant time × treatment interaction effect ($F_{(8, 84)} = 0.931$, $P = 0.495$). Tukey's post hoc test revealed a significant increase in the AD group compared to the control group on the second ($P < 0.01$) and third ($P < 0.05$) days. Oral administration of SEL resulted in a significant decrease in the AS group compared to the AD group on the second ($P < 0.05$) and third ($P < 0.05$) days of learning (Fig. 4d). However, the injection of PBS in the rats of the PBS group and administration of selegiline in the SEL group had no significant effect on the number of errors in searching for the hidden box over the 3 days of training compared to the control group ($P > 0.05$ for each comparison).

Furthermore, one-way ANOVA showed a significant difference in the time spent in the target zone on the probe day among the groups ($F_{(4, 35)} = 7.11$, $P < 0.001$). Tukey's post hoc test revealed a significant decrease in the AD group compared to the control group ($P < 0.01$), and a significant increase in the AS group compared to the AD group ($P < 0.05$, Fig. 4e).

Additionally, one-way ANOVA showed a significant difference in the number of errors in searching for the target hole on the probe day ($F_{(4, 35)} = 5.67$, $P = 0.001$). Therefore, the AD group had a significant increase compared to the control group ($P < 0.01$), and the AS group showed a significant decrease compared to the AD group ($P < 0.05$, Fig. 4f).

The Effects of SEL on the fEPSP Slopes and PS Amplitudes of DG Granular Cells Layer in AD Rats

Field potentials were recorded from the hippocampal DG after stimulation of the hippocampal PP. According to Fig. 5e, a sample of the evoked field potential in the DG was recorded before HFS delivery (stable baseline response) and after tetanus.

fEPSP slope was significantly affected by both time points ($F_{(3, 28)} = 123.5$, $P < 0.001$) and treatment ($F_{(4, 112)} = 15.37$, $P < 0.001$) in a two-way RM ANOVA (Fig. 5a). However, there was no significant time × treatment interaction effect ($F_{(12, 112)} = 1.795$, $P = 0.057$). Tukey's post hoc analysis indicated a significant decrease at different times of 5 ($P < 0.001$), 30 ($P < 0.001$), and 60 min ($P < 0.001$) after HFS in the AD group than in the control group. Oral administration of SEL prevented the decremental effect of Aβ on the slope of fEPSP in the AS group at different times of 5 ($P < 0.01$), 30 ($P < 0.05$), and 60 min ($P < 0.01$); so that their magnitudes were similar to animals in the control group. However, the injection of PBS in the rats of the PBS group and administration of selegiline in the SEL group had no significant effect at different times of 5,30, and 60 min after HFS on fEPSP slope compared to the control group ($P > 0.05$ for each comparison).

The mean percent fEPSP slope change during 60 min after HFS ($F_{(4, 35)} = 20.34$, $P < 0.001$) was significantly

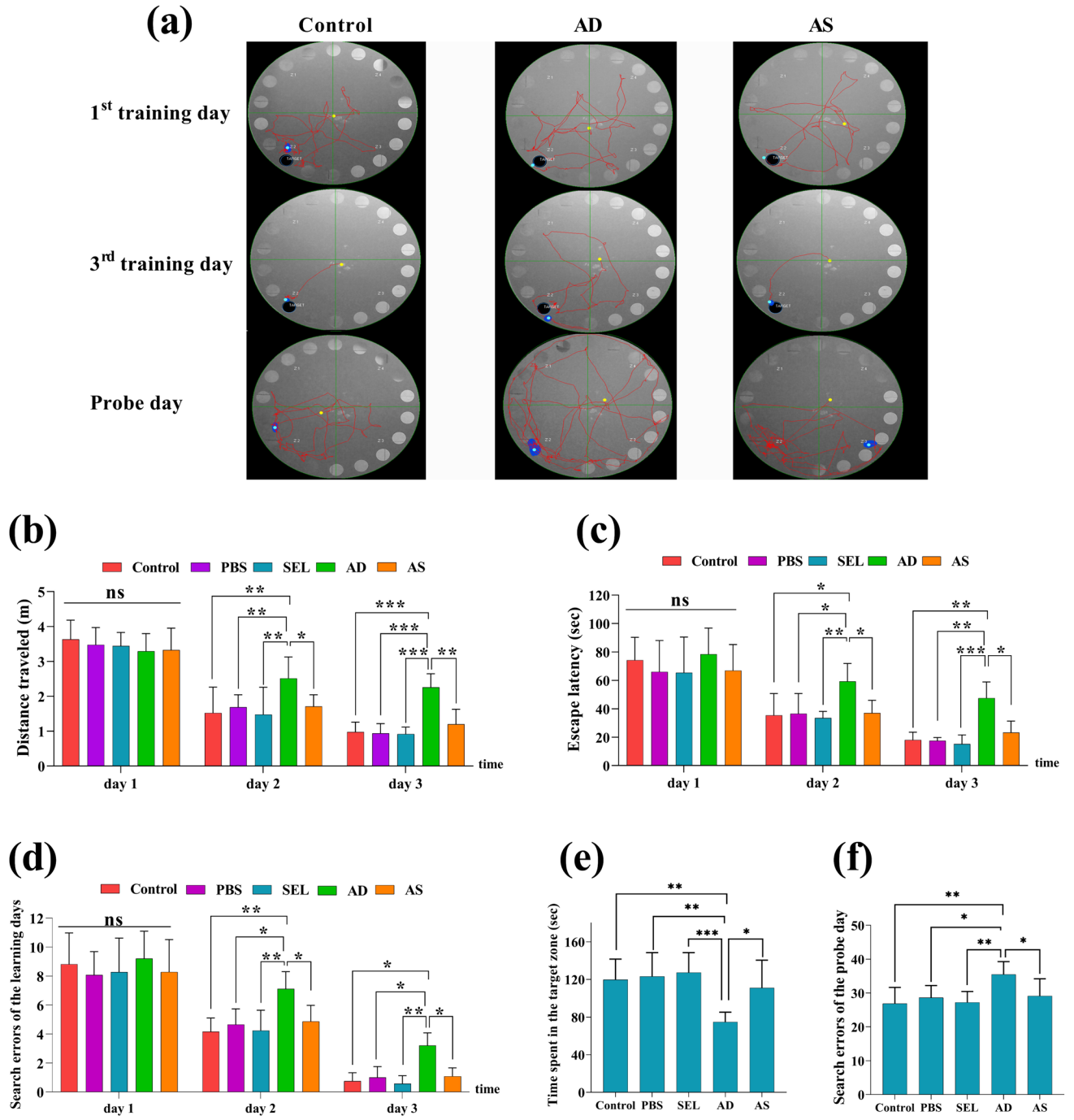

Fig. 4 The effects of selegiline on the BMT. Samples of recorded activities (**a**), distance traveled (**b**), escape latency (**c**), search errors of the learning days (**d**), time spent in the target zone (**e**), and search errors of the probe day (**f**) in the Barnes maze test. Data is presented as means ± SD of 8 animals per group (two- and one-way ANOVA, Tukey's post hoc test). ns, no significance; $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$

smaller in the AD group in comparison to the control group ($P<0.001$, Fig. 5c); This suggests that HFS did not considerably change the fEPSP slope and LTP induction was impaired in AD group.

According to the two-way ANOVA, the PS amplitudes of the granular cells layer are significantly influenced by time points ($F_{(3, 28)}=67.83$, $P<0.001$), treatments ($F_{(4, 112)}=18.04$, $P<0.001$), and time × treatment interaction effect ($F_{(12, 112)}=2.11$, $P=0.021$). Tukey's post hoc analysis indicated a significant decrease at different times of 5 ($P<0.01$), 30 ($P<0.001$), and 60 min ($P<0.001$) after HFS in the AD group than in the control group. Oral

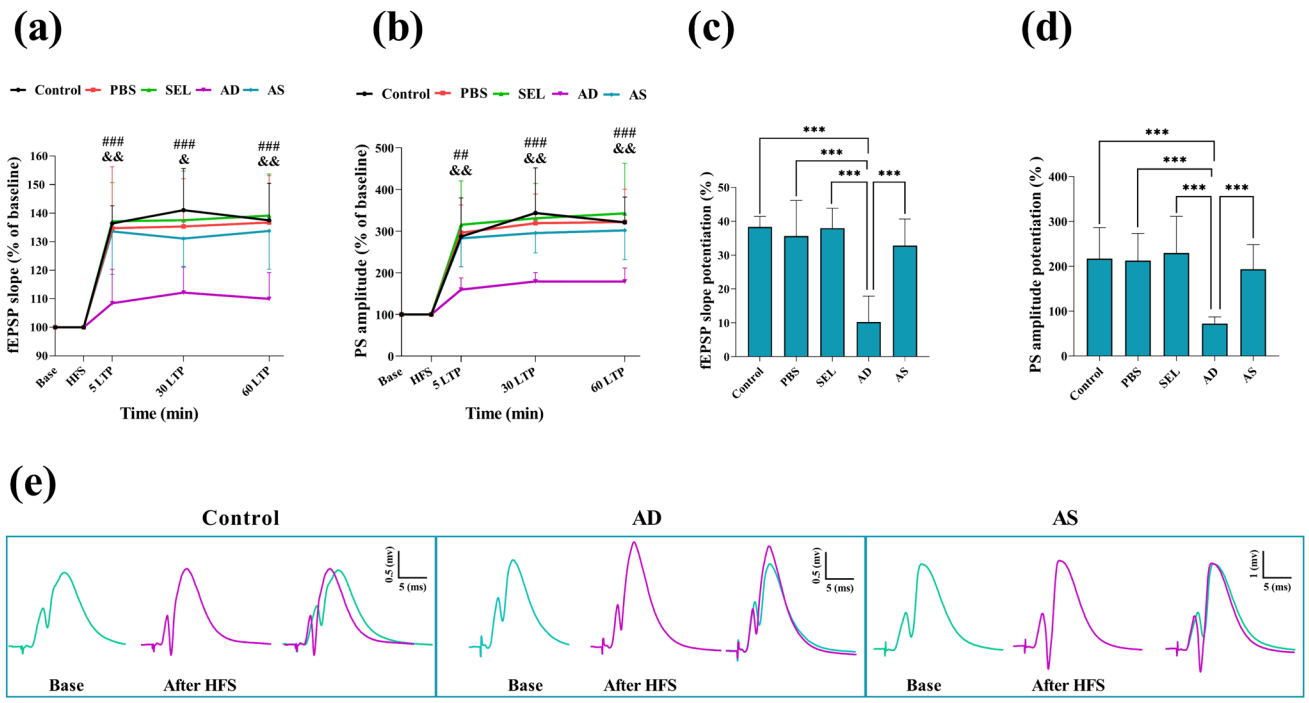

Fig. 5 The effects of selegiline (0.5 mg/kg/day for 30 consecutive days) on the evoked field potential in the hippocampal DG after HFS in AD rats. **a**, **b** Time course diagrams showing the changes in fEPSP slope and PS amplitude, respectively, prior to HFS and 5, 30, and 60 min after HFS of the PP (two-way RM ANOVA, Tukey's post hoc test). ##$P<0.01$, ###$P<0.001$ compared between the control group and AD group; &$P<0.05$, &&$P<0.01$ compared between AD group and AS group. **c**, **d** The percentage changes of fEPSP slope and PS amplitude during LTP induction, respectively (one-way ANOVA, Tukey's post hoc test). Data are expressed as means ± SD % of baseline of 8 animals per group. ***$P<0.001$. **e** Evoked field potentials in the DG of the experimental groups were measured before and 60 min after HFS

administration of SEL prevented these changes, so there was a significant difference in PS amplitudes in the AS group at different times of 5 ($P<0.01$), 30 ($P<0.01$), and 60 min ($P<0.01$) compared to the AD group (Fig. 5b). However, the injection of PBS in the rats of the PBS group and administration of selegiline in the SEL group had no significant effect at different times of 5,30, and 60 min after HFS on PS amplitude compared to the control group ($P>0.05$ for each comparison).

The mean percent PS amplitude change during 60 min after HFS ($F_{(4, 35)}=8.94$, $P<0.001$) was significantly smaller in the AD group in comparison to the control group ($P<0.001$, Fig. 5d); this suggests that HFS did not considerably change the PS amplitude and LTP induction was impaired in AD group.

Effect of SEL and Aβ on TTG and MDA in AD Rats

One-way analysis of variance showed a significant difference in the plasma levels of MDA among the groups ($F_{(4, 35)}=11.4$, $P<0.001$). Therefore, the AD group showed a significant increase compared to the control group ($P<0.001$). Additionally, the AS group had a significant decrease compared to the AD group ($P<0.05$, Fig. 6a).

Similarly, one-way ANOVA showed a significant difference in the plasma levels of TTG among the groups ($F_{(4, 35)}=11.13$, $P<0.001$). The AD group showed a significant decrease compared to the control group ($P<0.001$). Additionally, the AS group significantly increased compared to the AD group ($P<0.05$, Fig. 6b).

The Effect of SEL and Aβ on the Histological Changes in the Hippocampus

Hematoxylin & Eosin staining was conducted to confirm the histological changes in the hippocampus's DG and CA1 regions in the brains of the rats. As illustrated in Fig. 7a, a significant drop was found in the number of intact neurons of the hippocampal CA1 ($F_{(2, 9)}=77.43$; $P<0.001$) and DG ($F_{(2, 9)}=84.95$; $P<0.001$) regions of the AD group in comparison to the control group. Interestingly, the administration of SEL prevented neuronal death in the AS group. There was a significant difference in the number of intact neurons in the hippocampal CA1 ($P<0.001$) and DG ($P<0.001$) regions between the AS group and the AD group (Fig. 7b).

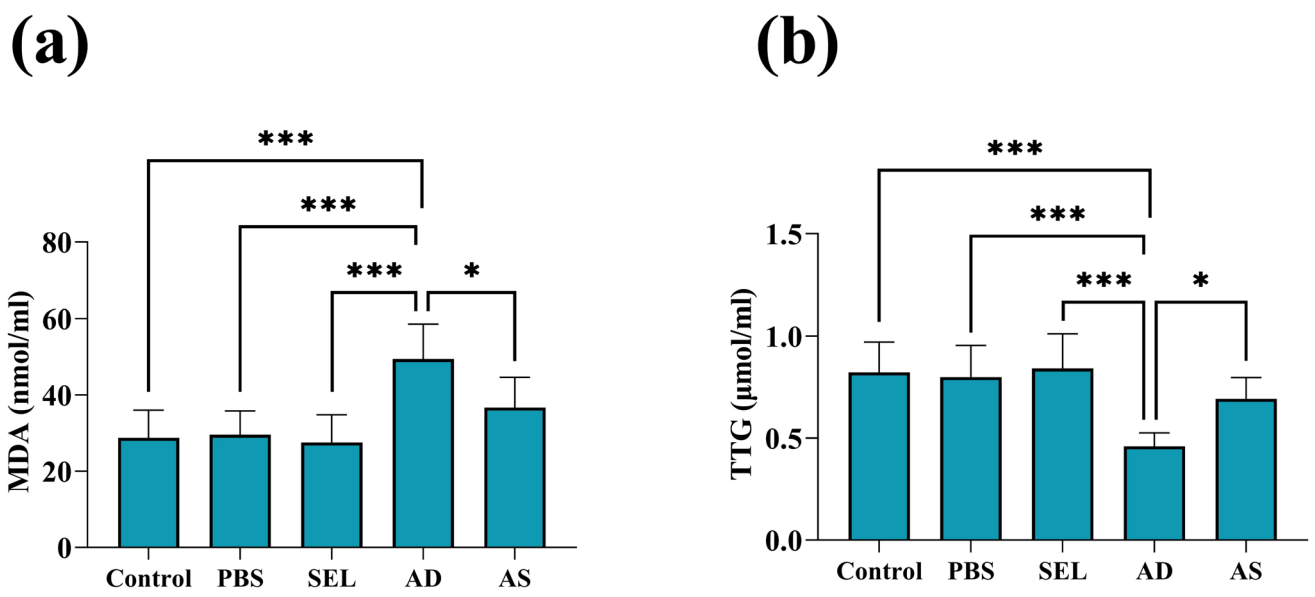

Fig. 6 The effects of selegiline (0.5 mg/kg/day, for 30 consecutive days) on the plasma parameters of malondialdehyde (MDA) (**a**) and total thiol group (TTG) (**b**) of AD rats using assay kits. Data is presented as means ± SD of 8 animals per group (one-way ANOVA, Tukey's post hoc test). *$P < 0.05$ and ***$P < 0.001$

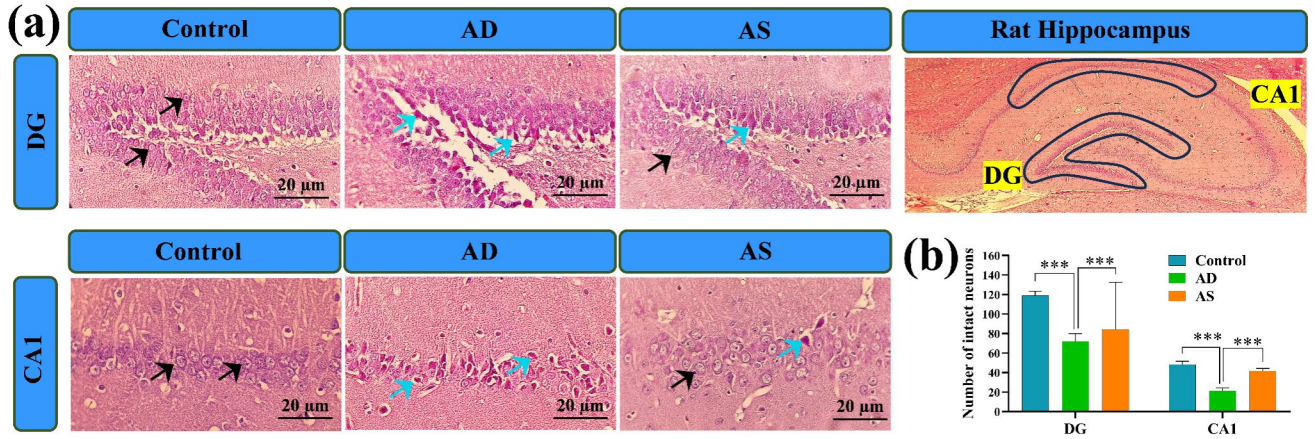

Fig. 7 Effects of selegiline and Aβ on histological changes in the hippocampal CA1 and DG regions of rats. **a** The figure illustrates intact neurons (identified by black arrows) and dark neurons (identified by blue arrows, H & E stain, × 40 magnification). **b** The quantitative data of the number of intact neurons. Data is presented as means ± SD of 4 animals per group (one-way ANOVA, Bonferroni post hoc test). ***$P < 0.001$

Discussion

This study's key findings are as follows: (1) SEL alleviated Aβ-induced spatial cognitive impairment in the rats. (2) SEL improved hippocampal synaptic plasticity deficit caused by Aβ in the rats. (3) SEL modulated the oxidant/antioxidant status in the Aβ-infused rats. (4) SEL ameliorated neuronal loss in the rat hippocampus. (5) Aβ and treatment with the SEL did not affect body weight.

The BMT used in the current work is a widely employed model in behavioral neuroscience to investigate spatial learning and memory abilities [49]. In the present study, the findings of BMT showed that Aβ injection leads to spatial learning impairment, as the time and distance traveled to reach the target box and the number of search errors increased in the rats during 3 days of learning. Moreover, the target zone occupancy was markedly alleviated in the probe trial, indicating impaired spatial memory in the Aβ-induced AD rats.

These findings were consistent with previous studies [50, 51]. However, SEL treatment reduced the distance traveled, the latency to reach the target box, and the number of search errors. On the other hand, treatment with SEL prolonged the target zone occupancy in the Aβ-induced AD rats. These results suggest that oral SEL treatment was able to improve spatial learning and memory impairments in the Aβ-infused rats. The findings of this study are consistent with previous studies, demonstrating that SEL could improve spatial learning and memory deficits in animal models of cerebral ischemia [17] and scopolamine-induced brain damage [21]. However, in an AD animal model, this is the first study to report that SEL is beneficial for spatial cognitive decline caused by Aβ.

LTP induction in the hippocampus is used to study the cellular basis of learning and memory [52]. LTP can be induced by activating N-methyl-D-aspartate (NMDA) glutamate receptors, which typically occur during the simultaneous activation of pre-synaptic and postsynaptic neurons [53]. In the present study, Aβ injection affected synaptic performance and inhibited LTP induction in the DG region of the hippocampus. The effects of Aβ injection on hippocampal synaptic plasticity were evident in the reduction of fEPSP slope and PS amplitude. There is considerable electrophysiological evidence from rodent models showing that Aβ injection can interfere with synaptic homeostasis and lead to suppression of LTP in the DG region of the hippocampus and cognitive impairments [54–56]. Strong evidence suggests that Aβ increases pre-synaptic calcium and alters glutamate levels in hippocampal synapses, leading to excitotoxicity [57]. The synaptic performance of the hippocampus can be compromised as a result of these detrimental changes caused by Aβ, leading to impairments in learning and memory mediated by the hippocampus. In this regard, it has been shown that spatial cognitive decline resulting from Aβ administration as an AD model is closely related to the suppression of hippocampal DG LTP [56]. However, treatment with SEL improved LTP impairment in the hippocampus of AD rats by increasing fEPSP slopes and PS amplitude. The possible mechanisms underlying SEL's protective action against hippocampal LTP impairment in AD rats can be attributed, at least in part, to the following mechanisms: (1) modulation of hippocampal dopaminergic transmission [28]; (2) regulation of Ca^{2+}/calmodulin-dependent protein kinase IIα (CaMKIIα) phosphorylation [58]; (3) reduction of tonic gamma-aminobutyric acid (GABA) inhibition [59]; (4) enhancement of exiatability of the different hippocampus subfields by augmenting basal firing rate, sodium/potassium ATPase (Na^+/K^+-ATPase), and protein kinase C activities [60]; and (5) stimulation of nitric oxide (NO) production [31]. However, the mechanisms mentioned above were not investigated in this study. Therefore, it is strongly recommended to investigate them in future research. While previous studies have demonstrated SEL's protective effects against hippocampal LTP impairment under both in vitro [59] and in vivo [28] conditions, our current study is the first to highlight SEL's neuroplastic properties in an AD model. Based on the present study, SEL may attenuate Aβ-induced LTP impairment in DG granule cells, potentially explaining its beneficial effects on spatial learning and memory impairments caused by Aβ.

Oxidative stress is a key pathological condition in neurological diseases and remains a major therapeutic target for AD [61]. Studies have shown that antioxidant factors improve hippocampal LTP induction and cognitive impairments resulting from AD [52, 62]. Consistent with previous studies [51, 63], in the present study, Aβ administration resulted in an imbalance of oxidative-antioxidant status in the plasma of rats, as evidenced by a decrease in TTG concentration (a non-enzymatic antioxidant) and an increase in MDA (a marker of lipid peroxidation) levels. Among all the antioxidants in the body, TTG constitutes a major part of the body's total antioxidants, helping protect cellular structures and functions against ROS [64, 65]. In lipid peroxidation, ROS attacks unsaturated lipids in the cell membrane, making the brain, which has high levels of unsaturated lipids, highly vulnerable to oxidative stress [62, 66]. Studies have shown that Aβ plaques are always co-localized with oxidized lipids in brain tissue samples affected by AD [67]. MDA is an important product of lipid peroxidation and is involved in the pathological cascade in AD [68]. Interestingly, treatment with SEL improved the oxidative/antioxidant balance in the plasma by increasing TTG concentration and suppressing the increase in MDA levels, indicating its antioxidant capacity. Consistent with these results, the antioxidant property of SEL has been previously reported [69, 70]. Therefore, it is speculated that SEL's ability to eliminate free radicals and prevent oxidative damage contributes to its protective effect against Aβ-induced impairments of hippocampal LTP and spatial learning and memory.

Neuronal loss is the outcome of various neurological diseases such as AD [71]. Some studies have shown that neuronal loss primarily occurs in regions with Aβ plaques, indicating a link between Aβ deposition and neuronal loss [72]. Furthermore, Aβ-associated neuronal loss can lead to behavioral impairments in AD [73]. Additionally, localized oxidative stress around the plaques has been shown to contribute to long-term toxicity and selective neuronal death in AD [71]. Consistent with previous studies [43, 51], Aβ injection in rats resulted in increased neuronal death in the hippocampal DG and CA1 regions. Interestingly, neuronal death was successfully prevented with SEL treatment in the hippocampus of Aβ-injected rats, which is in congruence with previous studies [17, 74]. The available evidence suggests that SEL's ability to inhibit Aβ plaque formation and neuronal death may be part of the explanation for its

protective effect against Aβ-induced deficits in LTP and spatial learning and memory.

Conclusions

The present study demonstrates, for the first time, that oral SEL treatment ameliorates spatial learning and memory deficits in AD rats, potentially through the modulation of oxidative status, reduction of neuronal death, and improvement of hippocampal LTP impairment. This study indicates that SEL may be a promising agent against AD-related cognitive decline. However, further research is needed to evaluate the mechanisms underlying SEL's protective effects against AD-related cognitive decline in detail, especially the mechanisms involved in its antioxidant properties.

Acknowledgements The current study was funded (Grant No. 99-371) by the Faculty of Basic Sciences, Bu-Ali Sina University, Hamadan, Iran. The authors are grateful to the staff of the Neurophysiology Research Center, Hamadan University of Medical Sciences for supporting this study.

Author Contribution Hamid Shokati Basir, Naser Mirazi, Alireza Komaki, Behnam Mohamadpour, and Abdolkarim Hosseini contributed equally to this work. All experiments were performed by Hamid Shokati Basir, Naser Mirazi, and Alireza Komaki. Hamid Shokati Basir, Naser Mirazi, Alireza Komaki, Behnam Mohamadpour, and Abdolkarim Hosseini wrote the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval Experimental methods and animal care were in accordance with the National Institutes of Health (NIH) and ARRIVE Guidelines and were approved by Bu Ali Sina University-Hamedan's Ethics Committee (Ethic code: IR.BASU.REC.1400.001).

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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