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Original Article

The Combined Effect of *Donepezil* and *Lovastatin* on the Electrical Activity of Hippocampal Pyramidal Neurons in a rat model of Alzheimer's disease

Running Title: *The Effect of Donepezil and Lovastatin on Pyramidal neuron in Alzheimer's disease*

Azade Eskandary[1*], Ahmad Ali Moazedi[2]

[1]Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran
[2]Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran

A R T I C L E I N F O

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***Corresponding author**
Ph.D., Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran.
Tel: +98-6133331045
E-mail
azade.eskandary@gmail.com

Abstract

Background: *Donepezil*, a noncompetitive acetylcholinesterase inhibitor, is prescribed to treat mild to moderate Alzheimer's disease but it only has moderate performance. Therefore, combination therapies are more effective. There is much evidence suggesting that statins have neuroprotective effects on neurological disorders including Alzheimer's disease. The present study aimed to investigate the combined effects of *Donepezil* and *Lovastatin* on the activity of the pyramidal neurons of the CA1 hippocampus.

Methods: In the present experiment study, adult male rats were divided into 3 groups: Nucleus Basalis Magnocellularis (NBM) lesion (which received electrically- induced lesion (0.5 mA, 3s) in NBM) group, NBM lesion + injection *Donepezil* 5mg/kg-*Lovastatin* 10mg/kg, NBM lesion+ injection *Donepezil* 15mg/kg-*Lovastatin* 30mg/kg. Spontaneous activity of pyramidal neurons in CA1 region to injection of *Donepezil*-*Lovastatin* was investigated in a rat model of Alzheimer's disease.

Results: The results of this study showed that electrical lesion of NBM leads to a decrease in the activity frequency of pyramidal neurons in the CA1 region. Administration of *Donepezil* 5mg/kg-*Lovastatin* 10mg/kg increased the frequency of pyramidal neurons in rat model of Alzheimer's disease.

Conclusion: The results of this study suggest that co-administration of *Donepezil*-*Lovastatin* (low doses) increases the activity of the CA1 pyramidal neurons in a rat model of Alzheimer's disease.

Keywords: Alzheimer's Disease, Single Unit Recording, Hippocampus, *Donepezil*, *Lovastatin*, Rat

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Introduction

Alzheimer's is a type of progressive brain disease that usually develops in old age. In Alzheimer's disease, the cellular structure of the neurons is damaged which affects memory and behavior (1). The formation of amyloid plaques around neuron cells as well as neurofibrillary filaments within brain cells are among the causes of this disease (2). Injuries to the brain caused by the formation of plaques of amyloid include inflammation of the brain tissue, the release of acetylcholinesterase from plaques, and the effect of amyloid deposition toxicity on brain cells (3). The early symptoms of Alzheimer's disease are severely impaired memory, especially spatial memory (4)). A decrease in acetylcholine due to the high release of acetylcholinesterase, which is a cause of Alzheimer's disease, impairs spatial memory (5).

Cholinergic projections of the basal forebrain/nucleus basalis magnocellularis (NBM) and the septum to the cortex and hippocampus have long been considered the main factor for memory (6). Several studies have reported that reduced hippocampal acetylcholine (as a result of aging or pharmacological) is associated with deficits in spatial memory (7). Since most neurons in the NBM are cholinergic, it seems that the reduction of cholinergic neurons due to NBM degradation can lead to memory loss (8).

Thus, based on this evidence, acetylcholinesterase (AchE) inhibitors such as *Donepezil* have been used to improve Alzheimer's-related cognitive decline (9). However, the use of acetylcholinesterase inhibitors only results in moderate remission. Therefore, multi-drug therapy is recommended to resolve this problem. Recently, the use of statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase, has been suggested as a therapeutic approach to reduce the cognitive symptoms of Alzheimer's disease (10). Neurological evidence suggests that this class of drugs has neuroprotective effects in Alzheimer's disease (11). In addition to reducing cholesterol, statins have several cholesterol-independent properties, including antithrombotic, anti-inflammatory, and stimulate nitric oxide (eNOS) synthesis (12)(). Statins also have antioxidant and anti-amyloidogenic properties (13). *Lovastatin* treatment increased the level of beta-amyloid precursor protein (s-APP-α) and decreased beta-amyloid production (14). In addition, *Lovastatin*, simvastatin, and atorvastatin repair cognitive deficits in traumatic brain injury (15). There is a relatively large gap between neuronal membrane properties and physiological and behavioral events. To do this, we need to be able to understand neuron activity. Extra Single-unit recordings are used to obtain valuable information about the structural features of the central nervous system. In neuroscience, the single-unit recording provides a method for measuring the electrophysiological responses of specific neurons using the microelectrode system (14). In Alzheimer's disease, most studies have focused on cognitive deficits and neuronal activity has been less studied. Therefore, the present study investigated the combined effect of *Donepezil* and *Lovastatin* on the activity of pyramidal neurons in the CA1 region of the hippocampus in a rat model of Alzheimer's disease.

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Material and Methods

In this experimental research, adult male Wistar rats (weight: 220±20 g) were obtained from the animal house of Ahvaz Jundishapur University of Medical Sciences. Animals were kept in a room at a constant temperature (24±2 0C) and light conditions (12 hours of light and 12 hours of darkness). In the process of the experiment, all the requirements of the Animal Ethics Committee were fulfilled (Ethics Code: EE/97.24.3.17933/scu.ac.ir).

Study drugs

Donepezil hydrochloride (Sigma-Aldridge), dissolved in saline (0.9%) as a vehicle, and *Lovastatin*, dissolved in dimethyl sulfoxide (DMSO) (5%), were used in this study. Control group animals received saline and DMSO. The drug was prepared immediately before injection and administered in a volume of 1 ml/kg.

Creating the Alzheimer's Model

The rats were anesthetized with ketamine hydrochloride (78 mg/kg, i.p., Alphasan) and xylazine hydrochloride (3mg/kg i.p. Alphasan, Netherlands) to develop Alzheimer's disease model and NBM rats were mutually ruined by electrical current (0.5 mA for 3 s) according to stereotaxic coordinates (AP= -1.3 mm, ML= ±2.8 mm, DV=-7.6 mm) (16). After the recovery period, rats were prepared for electrophysiological experiments. Rats were randomly divided into 3 groups to evaluate neuronal activity:

1) Lesion group (in which the NBM of animals was destroyed bilaterally with electrical lesion) + (saline – DMSO 5%)

2) NBM lesion + (*Donepezil* 15 mg/kg-*Lovastatin* 30 mg/kg)

3) NBM lesion + (*Donepezil* 5 mg/kg - *Lovastatin* 10 mg/kg)

Surgery

In the present study, a single unit recording of hippocampal pyramidal neurons was performed in anesthetized rats. Experiments were performed in a quiet room at a constant temperature (25±1 C). For this purpose, rats were anesthetized with urethane (1.5 g/kg, IP; Sigma-Aldrich, Germany). After anesthesia, to create a stable airway rats underwent tracheostomy surgery. In short, the hairs on the neck were removed. Then the muscles and soft tissues around the neck were removed until reached the trachea. A slit was created in the trachea and a polyethylene tube was inserted into the trachea. Then, the tracheostomy rats underwent stereotaxic devices (Stoelting, USA) for recording from the CA1 region. A two mm hole was created according to Paxinus Atlas (-3.8 mm AP, ±2.2 mm ML, -2.4mm DV) above the CA1 area of the hippocampus (17). Body temperature was maintained at 36-37 ° C during the recording period using a heating pad.

Extracellular single-unit recording

In this study, the effect of co-administration of *Donepezil* and *Lovastatin* was investigated on the spontaneous activity of pyramidal neurons in the CA1 area of the hippocampal. For this purpose, a tungsten microelectrode whit a 125 µm tip diameter and 5 MΩ resistances were gently moved to the CA1 region. The electrode was gently lowered to the hippocampal CA1 pyramidal cell layer with the aid of a microelectrode driver mounted on the stereotaxic arm, and the electrical potentials transferred to the tip were examined. To find spontaneous activity

pyramidal neurons, the electrode was inserted so high and low in the hippocampus that sometimes the tip was so close to a neuron that it could well receive its potential and sends it to the amplifier. Neurons with a frequency of 8 or less were identified as pyramidal neurons. So the neurons with size and shape stable signals and frequency of 8 or less were considered to check in this study. The neuron spikes were amplified by the amplifier (×10000 gain; 300 Hz, and 10 kHz for low and high filters, respectively) and were continuously displayed on the oscilloscope as a signal. The spike frequency was calculated and transmitted online in time bins of 1000 ms for the entire recording time by online sorter software (Spike; Science Beam, Tehran, Iran). The action potential was separated from the baseline activity by a window discriminator, which produced output pulses for the signal units based on the spike height, which counted the number of spikes per unit of time. In this study, the total recording time was 7200 s (bine size 1000 ms) which was stored on the hard disk and the average frequency was calculated by the computer (18).

After a pyramidal neuron with a steady frequency and amplitude and constant waveform emerged as a baseline record, the recording continued for 15 minutes. Then *Donepezil-Lovastatin* and their solvents were injected and recording continued for another 105 minutes. In this study, the discharge of each neuron was calculated in a time interval of 60 s bins using a data acquisition program to make a PSTHs (Peri- Stimulus Time Histograms) file with a time interval of 15 minutes before injection and 105 minutes after injection. Data were analyzed using an offline sorter (Spike; Science Beam, Tehran, Iran). Increasing or decreasing the activity of neurons than twice-fold the standard deviation of the baseline activity of neurons for three consecutive points was considered as an excitatory and inhibitory neuronal activity.

Histological confirmation

After the end of the electrophysiological record, the animals were deeply anesthetized using ketamine and xylazine. Their brains were removed and fixed in 10% formalin. After blocking, 20-µm slices were prepared near the recording electrode site. The slices were stained with H&E (Hematoxylin and Eosin). Then, place the electrodes recorded in hippocampal CA1 were studied by using a light microscope **(Figure 1).**

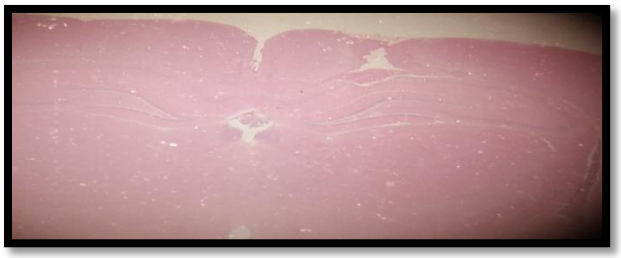

Figure 1: Position of recording electrode in hippocampal CA1 region

Statistical analyze

The data were analyzed by computer software SPSS (ver. 20). In order to perform statistical comparisons in the electrophysiology recording, the effect of drug and vehicle on the spontaneous activity of each neuron in each group was used Pair sample T-test in a 2-hour record. In addition, Graph pad Prism version 6.07 was used to illustrate the effect of the drug on the number of excitatory, inhibitory, and unaffected neurons. Data were expressed as Mean ± SD. A P-value less than 0.05 were statistically significant.

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Result

To investigate the effect of saline and DMSO on the activity of pyramidal neurons in the CA1 region, saline-DMSO was injected (IP; 1ml/kg for each vehicle) after baseline recording, and neuronal activity was recorded for another 105 minutes. Paired sample T-test of the spontaneous response of neurons to injection of saline and DMSO showed no significant increase in the firing frequency of neurons after injection compared to basal activity [(t= -1.042, df=13, P=0.317)] **(figure 2) (figure 3)**.

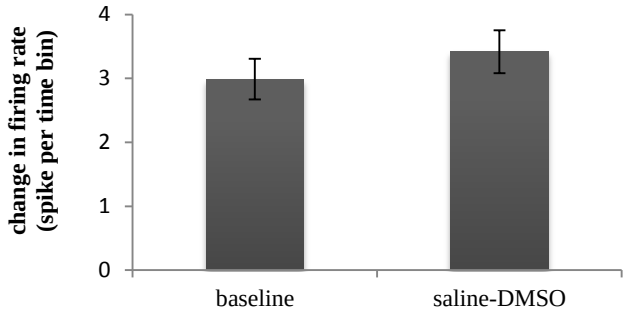

Figure 2: Effect of saline-DMSO on the firing frequency of the CA1 pyramidal neurons (P>0.05).

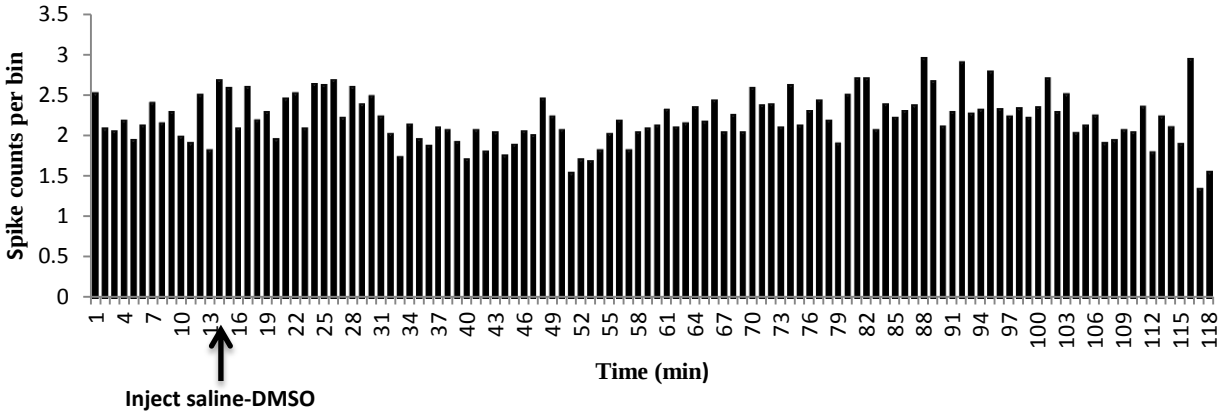

Figure 3: Histogram of firing pattern of CA1 pyramidal neurons before and after saline-DMSO injection

In this group, 14 neurons were recorded from 11 rats. In this experiment, co-administration of saline and DMSO excited 3 neurons, unaffected 9 neurons, and inhibited 2 neurons. Also, the mean increase in activity of pyramidal neurons in the hippocampal CA1 region showed that injection of saline -DMSO increased 81 to 121% activity in 3 neurons and decreased 53 to 57% activity in 2 neurons.

Statistical analysis in co-administration *Donepezil* 5 mg/kg - *Lovastatin* 10 mg/kg group (D5-L10) showed a significant increase in the firing frequency of neurons after injection compared to baseline activity [(t=-4.027, df=15, P=0.001)] **(figure 4)**.

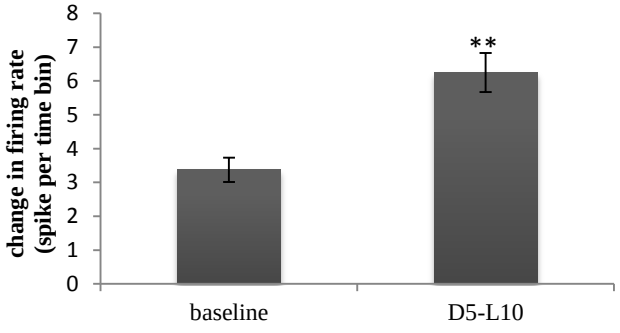

Figure 4: Effect of D5-L10 on the firing frequency of the CA1 pyramidal neurons (P<0.05).

In this group, 16 neurons were recorded from 10 rats and it was observed that co-administration of *Donepezil* 5 mg/kg and *Lovastatin* 10 mg/kg excited 11 neurons, unaffected 4 neurons, and inhibited one neuron **(figure 5) (figure 6)**. Increased activity of pyramidal neurons in the

CA1 region of the hippocampus showed that co-administration of drugs increased 71 to 111% activity in 5 neurons, increased in 3 neurons 121 to 181% activity, in 2 neurons increased 251 to 281% activity and in one neuron increased 300% activity.

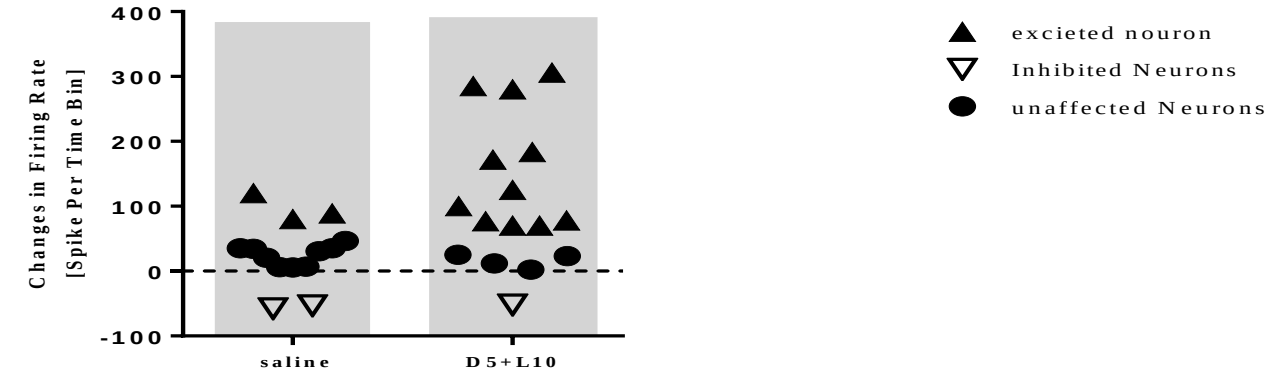

Figure 5: Scatterplot representing the response of pyramidal neurons to saline and *Donepezil* D5-L10 mg/kg injection

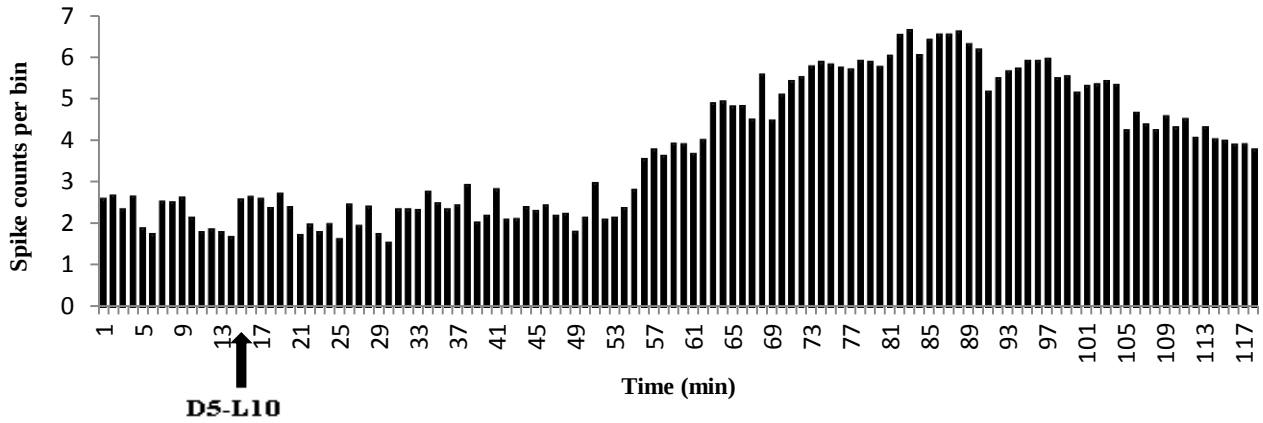

Figure 6: Histogram of firing pattern of CA1 pyramidal neurons before and after D5-L10 injection

In co-administration of *Donepezil* 15mg/kg - *Lovastatin* 30mg/kg (D15-L30), Paired sample T-test showed no significant increase in the firing frequency of neurons compared to baseline activity after injection [(t=-1.785,df=14, P=0.096)] **(figure 7)**. In this group, 15 neurons from 11 rats were recorded, and observed that co-administration of *Donepezil* 15mg/kg - *Lovastatin* 30mg/kg excited 4 neurons, unaffected 9 neurons, and inhibited 2 neurons **(figures 8,9)**. Increased activity of hippocampal CA1 pyramidal neurons showed that injection increased 70 to 100% activity in 2 neurons, and increased 120 to 190% activity in 2 neurons. Co-injection reduced 35 to 81% in 2 neurons.

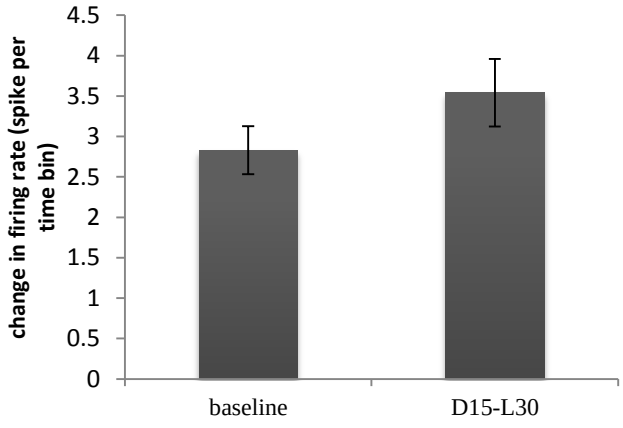

Figure 7: Effect of D15-L30 on the firing frequency of the CA1 pyramidal neurons (P>0.05).

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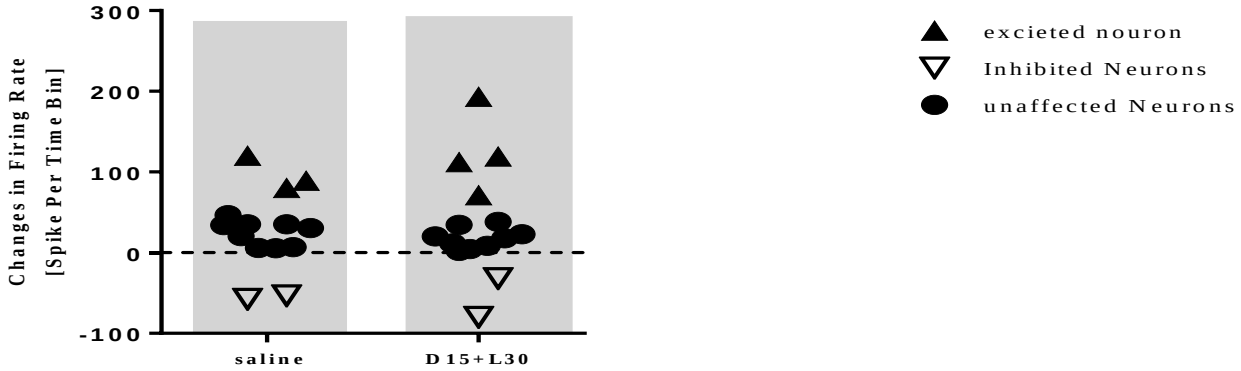

Figure 8: Scatterplot representing the response of pyramidal neurons to saline and *Donepezil* D15-L30 mg/kg injection

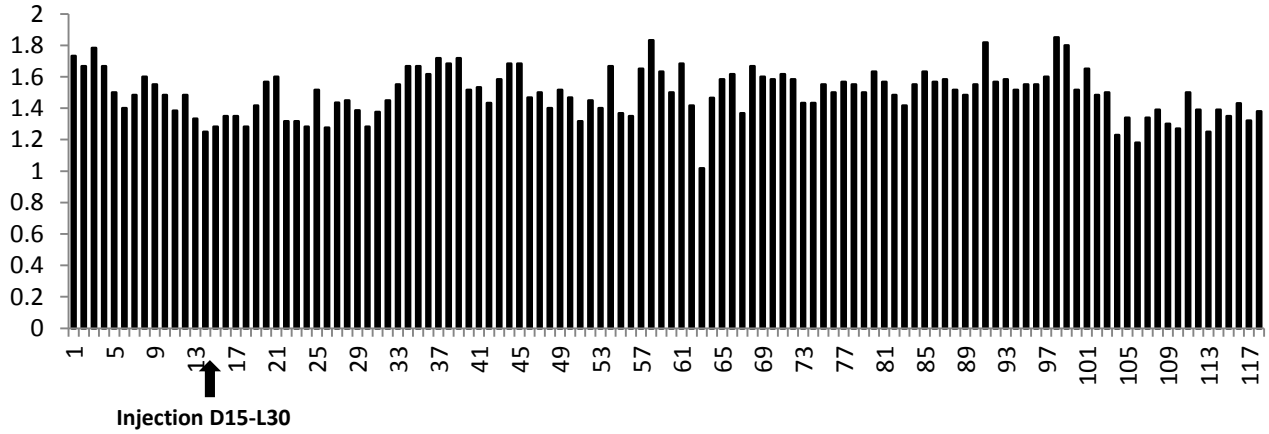

Figure 9: Histogram of firing pattern of CA1 pyramidal neurons before and after D15-L30 injection

Discussion

In this study, the effect of co-administration of *Donepezil-Lovastatin* was examined on spontaneous activity of pyramidal neurons in a rat model of Alzheimer's disease and it was found that *Donepezil* 5mg/kg - *Lovastatin* 10mg/kg has positive effects and increased spontaneous activity of pyramidal neurons in CA1 region of the hippocampus but both drugs at higher doses (D15-L30) had no significant effect on neuronal activity. In the present study, the degradation of NNB cholinergic neurons decreased the frequency of hippocampal pyramidal neurons. NBM cholinergic degradation patterns are used to study the role of the cholinergic system in cognitive functions and perception and it points to cognitive deficits in Alzheimer's disease. The NBM is the primary source of cholinergic projection to the cortex and plays an important role in cognitive processes (19). The cholinergic system, along with other nervous systems is responsible for storing and retrieving information in memory. Since most neurons in the NBM are cholinergic, it seems that the reduction of cholinergic neurons due to NBM degradation can lead to a decrease in the activity of hippocampal pyramidal neurons and memory loss (8).

Drugs that emphasize only one aspect may not be effective for the treatment of neurological syndromes involving several pathologic factors. In the meantime, the relationship between several drugs or combination therapy is widely used. The

components of combination therapy that separately affect individual neuronal systems may be more useful than singular therapies. Studies have shown that several combinations of *Donepezil* with other compounds had a potent effect on cognitive functions (20). In the present study, the combination of *Donepezil* and *Lovastatin* (low dose) increased the activity of the hippocampal pyramidal neurons. Cholinergic stimulation of pyramidal neurons in the CA1 region of the hippocampus acts almost through muscarinic receptors and increases excitatory ability is mediated by regulation of synaptic behavior and intrinsic properties of the membrane. Activation of muscarinic receptors induces depolarization and enhances the excitation of pyramidal neurons of the CA1 region by activation of cationic conductance as well as inhibition of potassium activity (21). Also, it has been shown that cholinergic stimulation leads to enhanced conductance of high voltage-activated calcium channels (22). Several studies have shown that acetylcholine release and mAchR activation lead to enhanced glutaminergic synaptic responses in the central nervous system (23). In the hippocampus, muscarinic receptor agonists promote NMDA receptor-dependent LTP induction at synapses between CA1 and CA3 pyramidal neurons (24).

Besides, several studies showed that lipophilic statins, such as *Lovastatin*, decrease acetylcholinesterase activity in the frontal cortex of rats, leading to increased levels of acetylcholine in the synaptic cleft (12). Also, it was reported that *Lovastatin* leads to the up-regulation of α7-nAchRs, which in a cholesterol-independent mechanism results in increased production of α-APPs during APP processing and resulting in a decrease in Aβ levels (25)(). Studies showed that treatment of brain slices with simvastatin (a member of the statins family) resulted in increased presynaptic glutamate release and increased amplitude of LTP-dependent NMDA receptor. Isoprenoid supplements (farnesyl pyrophosphate) suppress the effect of simvastatin on glutamate release and LTP enhancement. The results of this study suggested that simvastatin resulted in increased LTP in the hippocampal slices by inhibiting the production of farnesyl pyrophosphate (26). Also, statins have been reported to directly increase NO production and upregulation of eNOS. In addition, studies have shown that statins increase eNOS activity by activating the PI3K / Akt pathway. Numerous studies in recent years indicate the critical role of NO in neurophysiological processes in learning and memory. Inhibition of the NO system damages the memory of rats while stimulating NO production improves cognitive function in Alzheimer's patients. NO probably acts as a secondary reversal messenger in LTP formation at the molecular level of learning and memory processes (27).

The results of this study show that NMB degradation as an Alzheimer's disease model reduces the excitability of these neurons by altering the electrophysiological properties of hippocampal CA1 pyramidal neurons in the form of reduced frequency. However, treatment with *Lovastatin* and *Donepezil* (low dose) increased the excitability of hippocampal CA1 pyramidal neurons and could improve cognitive impairment

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in Alzheimer's disease. Administration of high doses simultaneously antagonizes the stimulating effect of *Donepezil* and *Lovastatin* on the activity of pyramidal neurons. In this part of the research, no report was found for further investigation to provide possible mechanisms caused by the combined injection of these drugs. How *Donepezil* interacts with *Lovastatin* to induce effects is not clear and requires further research.

Conflict of interest: The authors declared no conflict of interest.

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Ethical considerations: This study was reviewed and approved by the Ethics Committee of the Shahid Chamran University, Ahvaz, Iran. (Registration Code: EE/97.24.3.17933/SCU.ac.ir).

Authors' contribution: All authors contributed to preparing this article.

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