Research Paper: Differential Effect of Amyloid Beta1-40 on Short-term and Long-term Plasticity in Dentate Gyrus of a Rat Model of Alzheimer Disease

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ABSTRACT

Introduction: Synaptic plasticity is inappropriately affected by neurodegenerative diseases, including Alzheimer Disease (AD). In this study, we examined the effect of intrahippocampal amyloid-beta ($A\beta1-40$) on dentate gyrus Long-term Potentiation (LTP) and presynaptic short-term plasticity in a rat model of AD.

Methods: The experimental groups in this research included the control with no treatment, sham-operated receiving the vehicle (normal saline), and Aβ-lesioned groups. For modeling AD, aggregated Aβ1-40 (10 μg/2 μl on each side) was injected into the hippocampal CA1. Three weeks later, Population Spike (PS) amplitude and slope ratios were determined at different Inter-pulse Intervals (IPI) of 10, 20, 30, and 50 ms as a valid indicator of the short-term presynaptic facilitation and/or depression. In addition, PS amplitude and slope were taken as an index of long-term synaptic plasticity after application of High-frequency Stimulation (HFS) to induce LTP in the medial perforant-dentate gyrus pathway.

Results: No significant differences were noted amongst the experimental groups regarding fEPSP slope and paired-pulse indices as indicators of short-term plasticity. In contrast, fEPSP slope and PS amplitude significantly decreased following the application of HFS in Aβ-injected group. In addition, there was no significant difference between the control and sham-operated groups regarding the mentioned parameters.

Conclusion: Findings of this study clearly demonstrated that microinjection of Aβ1-40 into the CA1 could impair LTP in dentate gyrus but could not modify short-term plasticity.

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Highlights

● AD is a neurodegenerative disease with high prevalance in the elderly.

● The main reason of AD is Brain extracellular deposition of Amyloid-Beta (Aβ) peptide plaques

● Two kinds of synaptic plasticity are Short-term Plasticity (STP) and Long-term Plasticity or Potentiation (LTP)

● According to experimental studies loss of cognitive performance in AD are somewhat due to alterations in presynaptic functions and disability of the synapse to act normally.

Plain Language Summary

Alzheimer Disease (AD) is a neurodegenerative disease in the elderly with high prevalence that finally leads to dementia and death. Amyloid-Beta (Aβ) peptide plaques is the key pathologic hallmark of patients with AD. In experimental models it is reported that Aβ alone even before the development of plaques could cause neuronal injury and death in affected patients. Experimental studies indicate that loss of cognitive performance in AD are somewhat due to alterations in presynaptic functions and disability of the synapse to act normally. By progression of the disease, the number of synapses relative to neuronal population decreases, and this imbalance is associated with memory loss. This study was designed to examine the effect of intrahippocampal Aβ1-40 on Dentate Gyrus (DG) LTP and presynaptic short-term plasticity in a rat model.

1. Introduction

Alzheimer Disease (AD) is a neurodegenerative disease in the elderly with high incidence in the human society that at its late stages, finally leads to dementia and death (Crous-Bou, Minguillon, Gramunt, & Molinuevo, 2017; Lane, Hardy, & Schott, 2018). Brain extracellular deposition of Amyloid-Beta (Aβ) peptide plaques is the key pathologic hallmark of patients with AD (Magalingam, Radhakrishnan, Ping, & Haleagrahara, 2018). Aβ due to its neurotoxic properties is responsible for neuronal degeneration and synaptic loss in AD (Reiss, Arain, Stecker, Siegart, & Kasselman, 2018; Vargas, Cerpa, Munoz, Zanlungo, & Alvarez, 2018). Accumulating evidence in experimental models of AD and in affected patients strongly indicates that Aβ alone even before the development of plaques could cause neuronal injury and death (Parihar & Brewer, 2010). Synaptic plasticity is the capability of synaptic structures to alter the efficacy and/or strength of the synaptic transmission. In this respect, alterations in synaptic efficacy are suggested to play a key role in learning and memory processes (Esmaeili Tazangi, Moosavi, Shabani, & Haghani, 2015).

Two kinds of synaptic plasticity have been introduced, i.e. Short-term Plasticity (STP) using paired-pulse stimulation protocol (Moghaddam, Baluchnejadmojarad, Roghani, Goshadrou, & Ronaghi, 2013; Ohno et al., 2011) at appropriate inter-stimulus intervals (ISIs) that reflects the probable release of the presynaptic neurons with a spontaneous decay of conductance level, and Long-term Plasticity or Potentiation (LTP) using a tetanic stimulation protocol (high-frequency stimulation, HFS) that is responsible for the memory formation in humans (Ohno et al., 2011). Regarding STP, it can occur as Paired-Pulse Facilitation (PPF) or Paired-Pulse Depression (PPD), and their generation in the hippocampus is strongly related to the location of stimulation, stimulus strength, and the time between the two successive stimuli (Ohno et al., 2011). PPF is due to inward calcium current through presynaptic structures (Nicoll & Malenka, 1999; Staubli, 1992) and PPD is attributed to the desensitization of AMPA receptors in addition to modulation of the GABAergic system (Li, Vigh, & von Gersdorff, 2007; Ohno-Shosaku et al., 2011; Unichenko, Myakhar, & Kirischuk, 2012).

Experimental studies have demonstrated that loss of cognitive performance in AD are somewhat due to alterations in presynaptic functions and disability of the synapse to act normally (Fernandez-Fernandez, Rosenbrock, & Kroker, 2015; Lee et al., 2012; Yang, Wang, Wang, Justice, & Zheng, 2009). In moderate deterioration of cognitive ability, the number of active synapses in the hippocampus decreases with counterbalancing through increasing the dimension of synapses. Finally, with the progression of the disease, the number of syn-

apses relative to neuronal population decreases, and this imbalance is associated with memory loss (Giralt et al., 2017; Kawano et al., 2017; Vilella et al., 2017). However, the detailed pathogenic mechanisms that are responsible for the occurrence of these changes are not well-defined. Hippocampal LTP is a well-defined kind of synaptic plasticity that its deficit could lead to memory decline (Babri et al., 2014; Freir, Costello, & Herron, 2003). The effect of Aβ on short-term presynaptic facilitation and/ or depression has not been well identified. Considering different forms of Aβ (with varying degrees of neurotoxicity) and different sites of injection (i.e. intracerebral or intracerbroventricular), this study was designed to examine the effect of intrahippocampal Aβ1-40 on Dentate Gyrus (DG) LTP and presynaptic short-term plasticity in a rat model of AD using HFS and paired pulse stimulation protocols.

2. Materials and Methods

2.1. Animals

Male albino Wistar rats were obtained from the laboratory animal breeding center of Iran University of Medical Sciences (IUMS), Tehran, Iran (age: 11-13 weeks; body weight: 250-290 g). The rats were housed in Plexiglas cages with woodchip bedding in groups of 3-4 per cage at standard room temperature (21-23ºC) and a humidity of 40-50% under 12 h light-dark cycle (the light period started on 07:00 a.m.). Food and water were freely provided. All practical interventions regarding animals and their care were done in compliance with guidelines stipulated by the National Institutes of Health of USA for the care and use of experimental animals and those of IUMS (Tehran, Iran).

2.2. Materials

Aβ1-40 was purchased from Sigma (USA).

2.3. Aβ (1-40) preparation

Aβ1-40 was dissolved in normal saline at a concentration of 2 mg/ml and stored at -20°C. Aggregation of Aβ1-40was done by in vitro incubation at 37°C for 72 h.

2.4. Experimental procedure

The rats (n=18) were randomly allocated and grouped into three experimental groups, including the control, sham, and Aβ1-40 groups. The sham group received was injected with an equivalent volume of normal saline. On the day of surgery, animals (n = 6 per group) were anesthetized with an i.p. injection of ketamine-HCl (100 mg/kg) and xylazine (10 mg/kg). The rats were fixed in a stereotaxic apparatus and according to the Paxinos' brain atlas, the scalp was incised at midline and small burr holes were made at appropriate sites bilaterally (AP -3.8, ML ±2.2, DV -2.7). Then, the Aβ1-40 solution (10 μg/ 2μl) was bilaterally injected into the dorsal hippocampus over 5 min by a Hamilton microsyringe. Sham-operated rats received the vehicle solution. The skin was then sutured and the animals were maintained to recover in a warm box before returning to their home cages.

2.5. Electrophysiological study

Three weeks following intracerebral microinjection of Aβ or vehicle, rats were deeply anesthetized with urethane (1.7-1.8 g/kg b.w., i.p.) and their heads were placed in a stereotaxic frame. A homeothermic device was used to sustain body temperature at 36.5°C. Then, the cranium was exposed and two burr holes were drilled for the insertion of stimulating and recording electrodes. Bipolar stainless steel stimulating electrode with a diameter of 0.125 mm (A-M Systems, USA) was placed in the medial perforant pathway (4.2 mm lateral to the lambda, 3.2 mm ventrally) and a stainless steel recording electrode was placed in the DG with the maximum response (3.8 mm posterior and 2.2 mm lateral to the bregma).

Evoked field potentials were recorded from DG cells after stimulation of the medial perforant pathway. Recording of field potentials began at least 15 min following the insertion of the stimulating and recording electrodes. Applied stimuli were biphasic square waves (a width of 200 ms). Extracellular field potentials were amplified 1000x, digitized at 10 kHz, and filtered at a band of 0.1 Hz-10 kHz with the aid of a differential amplifier. Signals were passed through the A/D interface (Science Beam Co., Iran) to a computer, and data were analyzed using the e-probe software. Stimulation intensity was adjusted at a level to evoke 40% of the maximal response (field Excitatory Post-Synaptic Potential (fEPSP) and Population Spike (PS)). Also, PS amplitude was measured as the average of the potential difference between the peak of the first positive wave and the peak of the first negative deflection as well as the potential difference between the peak of the second positive wave and the peak of the first negative deflection. Meanwhile, the fEPSP slope, as an index of synaptic efficacy, was determined as the maximum slope between the initial point of fEPSP and the first positive wave.

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2.5.1. Input/output functions

Input-Output (I/O) functions were obtained by graded variation of the stimulus intensity (100-1100 μA) for the assessment of synaptic efficacy before LTP induction. fEPSP and PS were triggered in DG using 0.1 Hz stimulation and five evoked responses were averaged at each current intensity.

2.5.2. Paired-pulse response

After recording for 40 min, paired-pulse depression/facilitation was determined. The response to paired-pulse stimulation was subsequently recorded and delivered at 40% of maximal stimulus intensity with the Inter-Pulse Intervals (IPI) of 10, 20, 30, and 50 ms. For each IPI, 10 consecutive evoked responses were averaged. The population spike amplitude ratio [ratio of the second population spike amplitude to the first population spike amplitude; PS2/PS1%, Paired-Pulse Index (PPI)] and the fEPSP slope ratio [second fEPSP slope/first fEPSP slope (%); fEPSP2/fEPSP1%] were determined at various inter-stimulus intervals.

2.5.3. LTP

After stable baseline recording for at least 30 min, LTP was induced through the delivery of HFS (10 trains of 15 pulses at 200 Hz separated by 10 s), and after the tetanic stimuli, the baseline stimulation was resumed and recording continued for at least 90 min, and 5 consecutive evoked responses were averaged at stimulus intervals of 10 s.

2.6. Data analysis

All results are shown as Means±SEM For electrophysiological comparison, data were analyzed using One-Way Analysis of Variance (ANOVA), one-way repeated measures ANOVA, and Tukey post-hoc test. In addition, a p-value of less than 0.05 was considered significant.

3. Results

3.1. Input/output (I/O) functions

Stimulus-response curves were obtained from the DG following the stimulation of the medial perforant pathway to assess the synaptic potency (Figure 1). In this respect, one-way repeated measures ANOVA showed that PS amplitude and fEPSP slope prior to application of paired-pulse stimulation and HFS protocols did not significantly differ between the groups ($F_{2,14}=1.94$, $P>0.05$).

3.2. Paired-pulse responses

As shown in Figure 2, the paired-pulse protocols were applied to the medial perforant pathway, and recording was obtained from the DG at different IPIs of 10, 20, 30, and 50 ms. One-way repeated measures ANOVA showed no significant differences regarding EPSP slope and paired-pulse indices amongst the experimental groups.

3.3. LTP

LTP responses were recorded from the DG of different groups (Figure 3). Statistical analysis of different time points before the application of HFS did not indicate a significant difference (baseline data for fEPSP slope and PS amplitude) among the groups. In other words, intrahippocampal bilateral microinjection of aggregated Aβ1-40 did not significantly affect baseline responses. In contrast, one-way repeated measures ANOVA indicated a significant difference amongst the groups for fEPSP slope ($F_{2,15}=1.15.3$, $P<0.01$) and PS amplitude
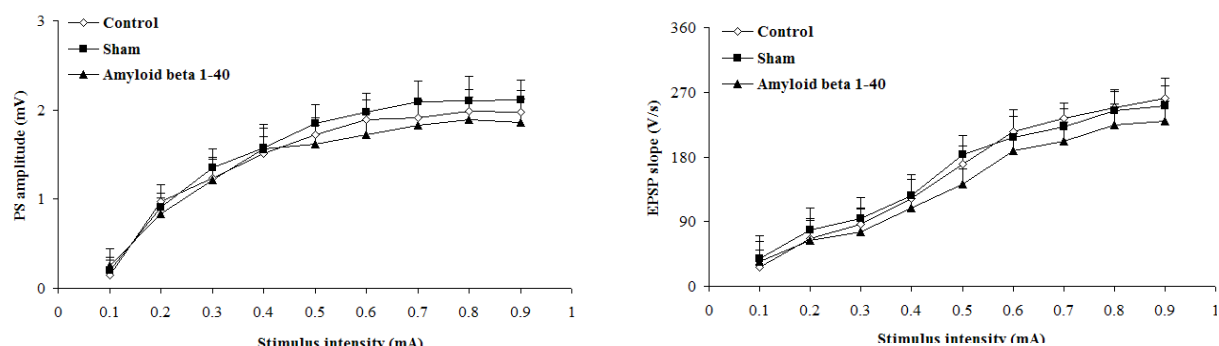

Figure 1. The input-output curves shown as field Excitatory Post-Synaptic Potential (fEPSP) slope and Population Spike (PS) amplitude in the dentate gyrus

Each point represents data obtained from 6 rats. Specimen recordings showed changes in baseline and LTP recordings 60 min after high-frequency stimulation HFS. Each recording is the average of 10 consecutive recordings at 100 s with an interval of 10 s. There was no statistically significant difference amongst the groups.
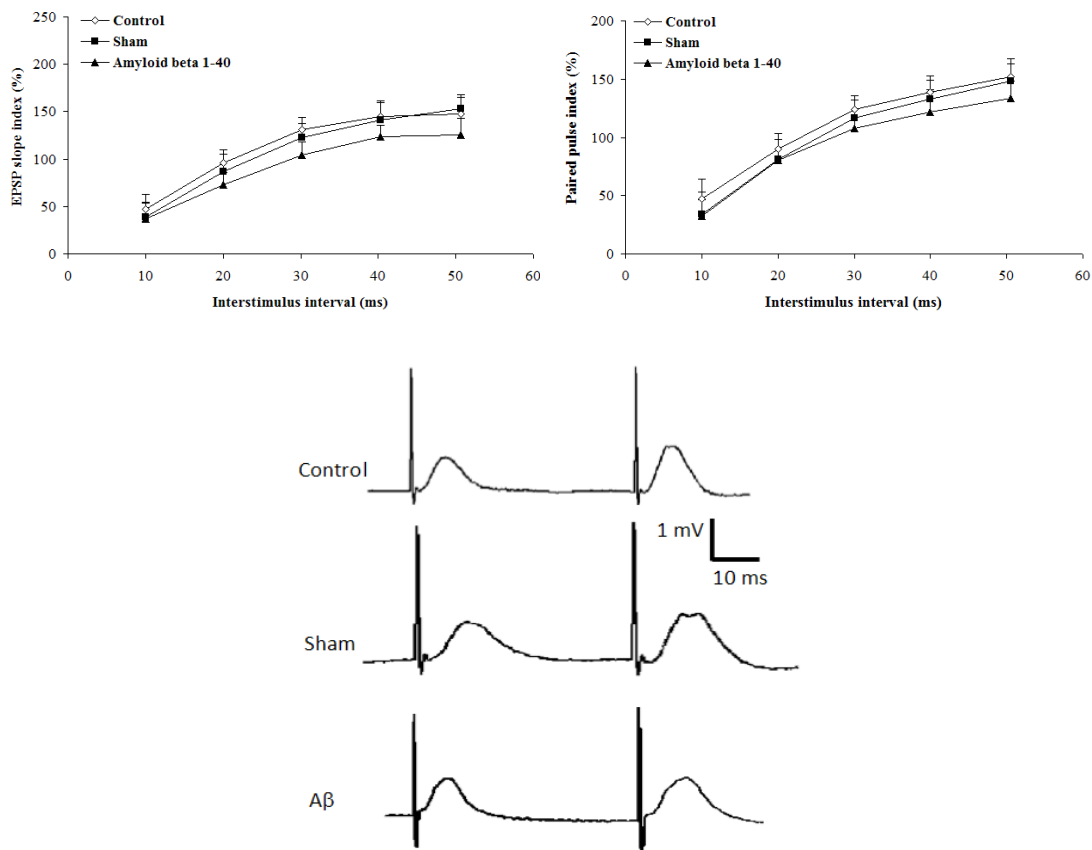
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Figure 2. The effect of Amyloid-Beta (Aβ1-40) on paired-pulse responses in the hippocampal dentate gyrus

At the intervals of 10, 20, 30, and 50, as shown by field Excitatory Post-Synaptic Potential (fEPSP) slope ratio (second response/first response ratio) and Population Spike (PS) amplitude ratio (second response/first response ratio) (n=6 per group) and traces recorded at dentate gyrus at an inter-stimulus interval of 50 ms. There was no statistically significant difference amongst the groups. Recording of the average of 10 consecutive PSs evoked by the paired stimuli in 100 s.

($F_{2,15}$=13.8, P<0.01) following the application of HFS. In this respect, the fEPSP slope was significantly lower in the Aβ1-40group than the control group at all time points ($F_{2,15}$=11.7,13.9, P<0.05-0.01). A similar significant difference was also found out for PS amplitude after the application of HFS amongst the groups ($F_{2,15}$=13.5, P<0.01). In this regard, PS amplitude was depressed and was significantly lower in the Aβ1-40group compared with the control group at all time points ($F_{2,15}$=14.7, P<0.01).

4. Discussion

The main objective of this study was to exactly determine the differential effect of the Aβ1-40 on DG short-term and long-term plasticity in a rat model of AD through intracerebral microinjection of aggregated Aβ1-40. Our findings demonstrated that long-term synaptic plasticity as LTP is severely impaired following the Aβ1-40 injection with no significant changes in short-term plasticity determined by a paired-pulse protocol.

In this respect, we observed that the intrahippocampal injection of Aβ1–40 severely dampens fEPSP slope and PS amplitude following the LTP protocol. Our findings regarding suppression of LTP were in agreement with earlier reports, which have reported that the exposure to soluble oligomers of Aβ could lower neuronal excitability and related synaptic plasticity and LTP in the hippocampal regions, including DG (Wang et al., 2002). Such oligomers do not significantly affect Long-Term Depression (LTD) associated with memory processes (Wang et al., 2002). In this regard, Aβ exposure could contribute to the pathogenesis of AD both by impairing LTP and memory formation at the cellular level and also by developing neuroplasticity imbalance in addition to the impaired capacity for neurons to recover (Wang et al., 2002). In contrast, Li et al. (2009) showed that the oligomers of Aβ could positively affect hippocampal LTD via disrupting neuronal uptake of the glutamate neurotransmitter (Li et al., 2009).
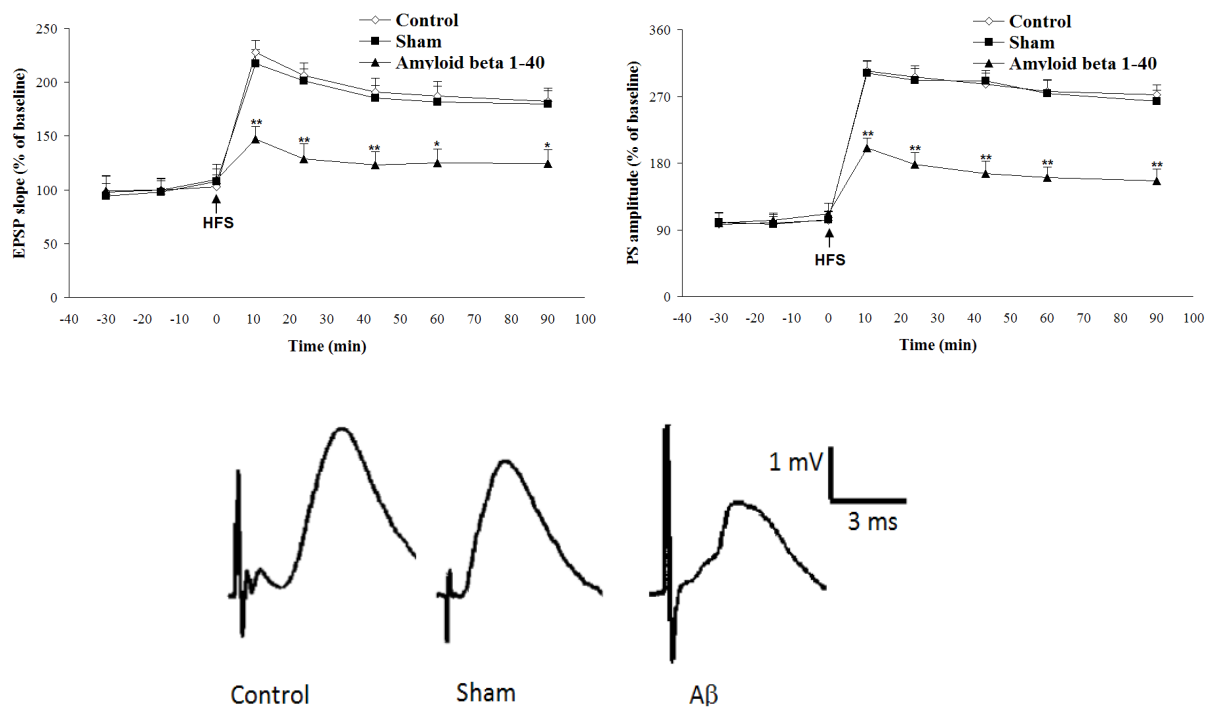
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Figure 3. The effect of amyloid-beta (Aβ1-40) on long-term potentiation (LTP) in the hippocampal dentate gyrus using High-Frequency Stimulation (HFS) as shown by field Excitatory Post-Synaptic Potential (fEPSP) slope and Population Spike (PS) amplitude and representative traces of evoked responses in the dentate gyrus of the rat hippocampus following stimulation of the medial perforant path; (n=6 per group); *P<0.05; and **P<0.01 versus the control group.

LTP is considered as a major synaptic mechanism that is valuable for the assessment of long-term synaptic plasticity in rats and mice. Post-tetanic LTP is postulated as a physiological form of synaptic plasticity and its appearance in cortical and subcortical regions is considered as a valuable tool for the assessment of learning and memory at the cellular and/or molecular levels (Bliss & Collingridge, 1993). According to previous reports, LTP induction and maintenance are significantly disturbed after the application of tetanic stimulation in animal models of AD (Lambert et al., 1998; Walsh et al., 2002) that is also consistent with our findings. Mechanistically, LTP is greatly dependent on N-Methyl- d-aspartic acid or N-Methyl- D-Aspartate (NMDA) receptors and is a widely-accepted mechanism for the occurrence of synaptic plasticity via the presynaptic release of the glutamate and consequent depolarization of post-tsynaptic target due to the activation of NMDA receptors and ensuing inward calcium currents. The neurotoxic peptide Aβ could target glutamate receptors, by which it exerts its synaptotoxic effects. In this regard, Aβ could decrease expression of NMDA receptors leading to a decrease in NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated synaptic transmission through enhancing receptors endocytosis (Hsieh et al., 2006).

In addition, brain nicotinic acetylcholine receptors are strongly engaged in learning and memory process through inducing LTP (Drever, Riedel, & Platt, 2011; Maurer & Williams, 2017). Experimental studies have indicated that Aβ fragments could lead to cholinergic dysfunction and consequent cognitive decline in individuals with AD (Nordberg, 2001). Aβ peptides could bind to some kinds of nicotinic receptors, which leads to the accumulation of intracellular Aβ and subsequent deficits in synaptic function (D'Andrea & Nagele, 2006), finally resulting in reduced release of acetylcholine, as an excitatory neurotransmitter, and consequently negatively affecting LTP. Furthermore, Aβ fragments could inhibit NMDA receptor-dependent synaptic neurotransmission partly through lowering inward calcium current via NMDA receptors, leading to a reduction in phosphorylation of calcium and calmodulin-dependent protein kinase II (CaMKII) followed by attenuation of the LTP process (Zhao, Watson, & Xie, 2004). In this regard, Lisman et al. in 2002 showed that CaMKII molecules are strongly involved in the occurrence of LTP in the hippocampal DG (Lisman, Schulman, & Cline, 2002).

In this research, we also assessed short-term plasticity in DG through the application of paired-pulse protocol. The paired-pulse ratio is correlated with the pre-

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synaptic release of neurotransmitters and is regarded as short-term plasticity (Fortune & Rose, 2002; Zucker & Regehr, 2002). Short-term plasticity is dependent on residual calcium in presynaptic terminals. An enhanced level of calcium following the application of the first stimulus could elevate the probability of neurotransmitter release as a result of the application of the second stimulus (Debanne, Guerineau, Gahwiler, & Thompson, 1996). In addition, GABAergic inhibitory interneurons could affect the excitability of the hippocampal granular and pyramidal cells through feed-forward and feed-back circuits, in this way modulating short-term plasticity related to presynaptic regions (Jiang, Sun, Nedergaard, & Kang, 2000). In our research, an Aβ1-40 exposure did not significantly affect PS amplitude and fEPSP slope due to the application of paired-pulse stimulation protocols at IPIs of 10, 30, 40, and 50 ms. Thus, it can be concluded that the reduction of PS amplitude and EPSP slope following HFS application is possibly unrelated to presynaptic function/activity and post-synaptic regions are affected to a greater degree following Aβ injection.

To conclude, our findings demonstrated that the long-term synaptic plasticity as LTP is severely impaired following Aβ injection with no significant changes in short-term plasticity determined by the application of a paired-pulse protocol.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information; Moreover, They were allowed to leave the study whenever they wish, and if desired, the results of the research would be available to them.

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Authors' contributions

All authors contributed equally in preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

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