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Effect of Aggregated β-Amyloid (1-42) on Synaptic Plasticity of Hippocampal Dentate Gyrus Granule Cells *in Vivo*

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a common neurodegenerative disorder in elderly people with an impairment of cognitive decline and memory loss. β-amyloid (Aβ) as a potent neurotoxic peptide has a pivotal role in the pathogenesis of AD. This disease begins with impairment in synaptic functions before developing into later neurodegeneration and neuronal loss. The aim of this study was to evaluate the synaptic plasticity and electrophysiological function of granule cells in hippocampal dentate gyrus (DG) after intracerebroventricular (i.c.v.) administration of aggregated Aβ (1-42) peptide *in vivo*. ***Methods:*** Animals were divided to control and Aβ (1-42) groups. Long-term potentiation (LTP) in perforant path-DG synapses was assessed in order to investigate the effect of aggregated Aβ (1-42) on synaptic plasticity. Field excitatory post-synaptic potential (fEPSP) slope and population spike (PS) amplitude were measured. ***Results:*** Administration of Aβ (1-42) significantly decreased fEPSP slope and PS amplitude in Aβ (1-42) group comparing with the control group and had no effect on baseline activity of neurons. ***Conclusion:*** The present study indicates that administration of aggregated form of Aβ (1-42) into the lateral ventricle effectively inhibits LTP in granular cells of the DG in hippocampus *in vivo*.

Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder among elderly people that is accompanied with a progressive cognitive decline and memory loss. The major hallmarks of this disease include neuronal degeneration and synaptic loss with presence of extracellular β-amyloid (Aβ) deposits and intracellular neurofibrillary tangles in different areas of cerebral cortex (Armstrong 1994). Aβ is a potent neurotoxic peptide and a major constituent of the senile plaques that initiates a cascade that leads to neural dysfunction and memory impairment. This peptide is a product of β-amyloid precursor protein (APP) cleavage and is found in the brain in two main forms with 40 and 42 amino acid peptides: Aβ (1-40) and Aβ (1-42), respectively (Drachman 2006, Jolas *et al* 2002).

The majority of investigations suggested that impairment in memory in AD begins with changes in hippocampal synaptic functions and then gradually progresses to neurodegeneration and neuronal loss in these patients (Selkoe 2002). Long-term potentiation (LTP) in the hippocampus is the most important form of synaptic plasticity that is considered as a cellular basis of learning and memory and provides an attractive means of detecting any changes in synaptic functions (Yun *et al* 2006). Previous studies have shown that intracerebroventricular (i.c.v.) administration of aggregated Aβ makes changes in LTP in the hippocampus and consequently leads to the cognitive dysfunction and impairment of spatial and non-spatial forms of learning and memory in rodents (Selkoe 2008, Trubetskaya *et al* 2003).

Interestingly, the effects of Aβ on LTP differ in various parts of the brain and there are conflicting results from previous studies about the effect of Aβ on synaptic plasticity and neuronal excitability. For example, result of a research showed that Aβ increases the N-methyl-D-aspartate (NMDA)-receptor mediated synaptic transmission and enhances LTP in rat hippocampus in vitro (Wu *et al* 1995a, Wu *et al* 1995b), and in an extracellular single unit recording administration of Aβ increased NMDA responses in the hippocampus (Molnár *et al*

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2004), while in other studies application of Aβ decreased neuronal excitability (Freir *et al* 2001, Yun *et al* 2006).

Previous reports also have demonstrated that the granule cell layer of dentate gyrus (DG), a sub-region of hippocampus, is involved in spatial learning and memory (Drapeau *et al* 2003, Kee *et al* 2007). Results of our previous study have shown that administration of exogenous aged Aβ (1-42) peptide in right lateral ventricle significantly impaired the spatial learning and memory in rats (unpublished data). We therefore examined the synaptic plasticity and electrophysiological function of granule cells in hippocampal dentate gyrus after i.c.v. injection of aggregated form of Aβ (1-42) peptide *in vivo*. For this purpose, we measured the fEPSP and PS as two components of the evoked field potential in the hippocampal DG in rats.

Materials and methods

Animals and treatments

Adult male Wistar rats weighing 300–350 g were obtained from Pasteur Institute of Iran. They were maintained at an ambient temperature of 22–24°C under a 12 hr light-dark cycle, with lights off at 7:00 pm. Food and water provided *ad libitum*.

Animals were randomly divided into two control and Aβ (1-42) groups (n=7 in each group). The Aβ (1-42) peptide fragment was purchased from Bachem (Switzerland). Congo red and poly l-lysine solution were obtained from Sigma (St. Louis, USA). Aβ (1-42) was dissolved in sterile double distilled water at a concentration of 2.25 mg/ml according to the manufacturer's instructions and 2 nmol in 4 µl was administered intracerebroventricularly (i.c.v.), as previously described (Dall'Igna *et al* 2007). To obtain the aggregated form, the peptide solution was placed in an incubator at 37 °C for 72 h.

Surgical procedures

The rats were anesthetized intraperitoneally with chloral hydrate (350 mg/kg) and placed in a Stoelting stereotaxic instrument (Stoelting Co., Illinois, USA). The scalp was incised and retracted and small hole was drilled at an appropriate location in the skull to allow the insertion of an injection cannula. Aβ or sterile double distilled water was then injected through a stainless steel cannula into the right lateral ventricle (AP: −0.8, ML: 1.6 and DV: 3.5 mm below dura) during 5 min by a Hamilton micro syringe and the needle was left in place for 5 min before it was slowly withdrawn. Coordinates were chosen based on Paxinos and Watson rat brain atlas (Paxinos and Watson, 2007).

Electrophysiological study

Two weeks after i.c.v. injection of Aβ or vehicle, rats were anesthetized with urethane (1.8 g/kg, i.p.) and their heads were fixed in a stereotaxic head-holder. A heating pad was used to maintain body temperature at 36.5±0.5°C. The skull was exposed and two small holes were drilled at the positions of stimulating and recording electrodes. The exposed cortex was kept moist by the application of paraffin oil. A concentric bipolar stimulating electrode (stainless steel, 0.125 mm diameter, Advent, UK) was placed in the perforant pathway (AP=−8.1 mm; ML=4.3 mm; DV=3.2 mm), and a stainless steel recording electrode was lowered into DG until the maximal response was observed (AP=−3.8 mm; ML=2.3 mm; DV=2.7–3.2 mm) (Paxinos and Watson 2007). In order to minimize trauma to brain tissue, the electrodes were lowered very slowly (0.2 mm/min). Extracellular evoked responses were obtained from the dentate granule cell population following stimulation of the perforant pathway. Extracellular field potentials were amplified (100×) and filtered (1 Hz to 3 kHz band pass) using a DAM80 differential amplifier (WPI, USA). Signals were passed through an analogue-to-digital interface (Powerlab/4SP, AD Instruments, Australia) to a computer, and data were analyzed using custom software. Stimulation intensity was adjusted to evoke about 40% of the maximal response of the population spike (PS) and field excitatory post-synaptic potential (fEPSP). The PS amplitude was measured as the difference in voltage between the peak of first positive wave and the peak of first negative deflection, and the fEPSP slope was measured as the maximum slope between the initial point of fEPSP and the first positive wave in order to measure synaptic efficacy (Reisi *et al* 2010). Stimulus–response or input/output (I/O) functions were acquired by systematic variation of the stimulus current (100–1000 A) in order to evaluate synaptic potency before induction of LTP. PS and fEPSP were evoked in the DG region using 0.1 Hz stimulation. Baseline recordings were taken at least 30 min prior to each experiment.

After ensuring a steady state baseline response, LTP was induced using high-frequency stimuli protocols of 400 Hz (10 bursts of 20 stimuli, 0.2 ms stimulus duration, 10 s interburst interval) at a stimulus intensity that evoked a PS amplitude and fEPSP of approximately 80% of the maximum response. All potentials employed as baseline before and after high frequency stimulation (HFS) were evoked at a stimulus intensity which produced 40% of this maximum (Reisi *et al* 2010). fEPSP slope and PS were recorded for the periods of 5, 15, 30, 45 and 60 min after HFS in order to determine any changes in the synaptic response of DG neurons. For each time-point, 5 consecutive evoked responses were averaged at 10 s stimulus interval.

Histology

On completion of electrophysiological study, rats were perfused transcardially with a cold 10% formalin solution and the brain was removed and post-fixed with the same formalin solution for 24 hr at room temperature and embedded in paraffin blocks. Subsequently, coronal sections with the thickness of 5 µm through the brain were cut using a microtome and mounted on poly-L-lysine–coated glass slides. The sections were used for evaluating the injection site and Congo red staining for detection of Aβ deposits in the hippocampus.

Aβ deposits

Modified high pH Congo red staining protocol for Amyloid was used for the detection of Aβ deposit in the brain slices. Briefly, Coronal sections were deparaffinized and hydrated in water (5 min), stained in Congo red solution (0.3% in 80% ethanol) for 10 min, rinsed in distilled water, quickly differentiated in alkaline alcohol solution, rinsed in tap water, counterstained with Gill's hematoxylin for 30 seconds, rinsed in tap water, dipped in ammonia water for 30 seconds or until sections turned blue, rinsed in tap water, dehydrated through 95% and 100% alcohol, cleared in xylene and covered with balsam and a covers lip. In this staining method the amyloid deposits and the nuclei were stained red and blue, respectively.

Statistical analysis

Two-tailed Student's *t*-test and two-way ANOVA with repeated measures were used for statistical comparison. A *p*-value of less than 0.05 was considered to be statistically significant. Data are expressed, as means±S.E.M for each group.

Results

Statistical analysis of data from time points before HFS did not show any difference in baseline fEPSP slope and PS amplitude between control and Aβ (1-42) groups. Therefore, i.c.v. administration of aggregated Aβ (1-42) had no effect on baseline activity of neurons. A two-way repeated measures ANOVA indicated that the fEPSP slope after HFS was significantly decreased in the Aβ (1-42) group with respect to the control group ($F(1,12)=18.34$; $p<0.01$) and this difference between two groups was significant in all time points ($p<0.01$; $n=7$) (Fig.1. A).

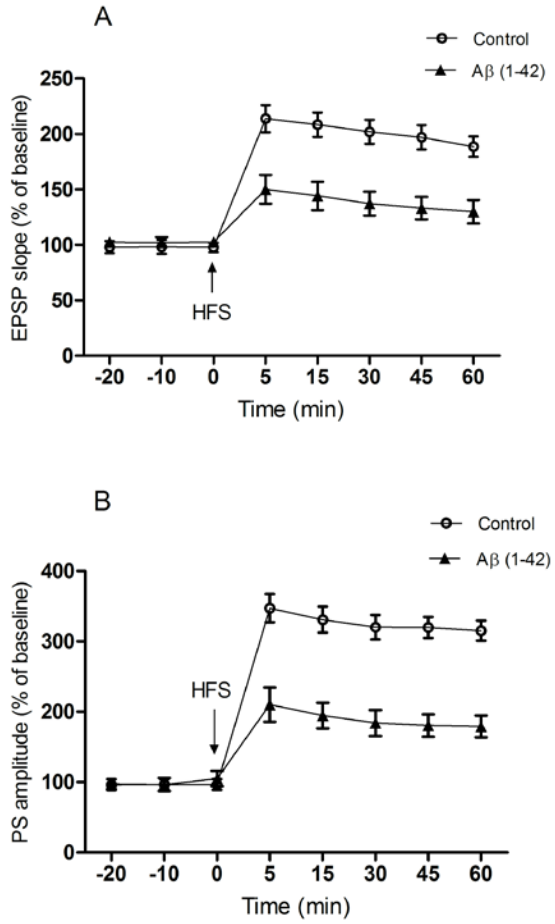

Fig. 1. The effect of aggregated Aβ on the synaptic response of DG granule cells following a 400 Hz HFS applied to the perforant pathway. (A) The Aβ did not affect the baseline fEPSP slope, but reduced the amplification of the fEPSP slope after 400 Hz HFS in comparison with the control group ($p<0.01$). (B) Aβ did not affect the baseline PS amplitude. However, after the 400 Hz HFS, Aβ reduced PS amplitude comparing with the control group ($p< 0.0001$). The data are shown as the mean±S.E.M.

Statistical analysis carried out with a two-way repeated measures ANOVA between the control and Aβ (1-42) groups revealed that Aβ (1-42) causes a significant decrease in the PS amplitude after HFS ($F(1,12)=32.99$; $p<0.0001$), and this difference was significant between two groups during 60 min after HFS ($p=0.001$ for 5^{th}, and 15^{th} min and $p<0.0001$ for 30^{th}, 45^{th} and 60^{th} min) (Fig.1. B). Sample traces for each group are illustrated in Fig. 2.

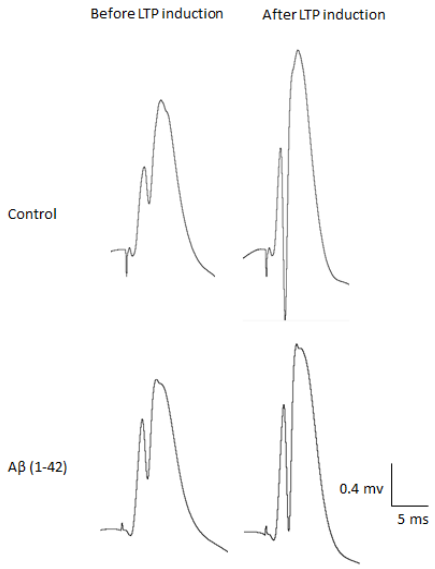

Fig. 2. Single traces recorded before and after induction of LTP in dentate gyrus granule cells of hippocampus.

Congo red staining of slices showed Aβ deposits between DG granule cells following i.c.v. injection of 2 nmol/4µl of aggregated Aβ (1-42)that were absent in control group (Fig. 3).

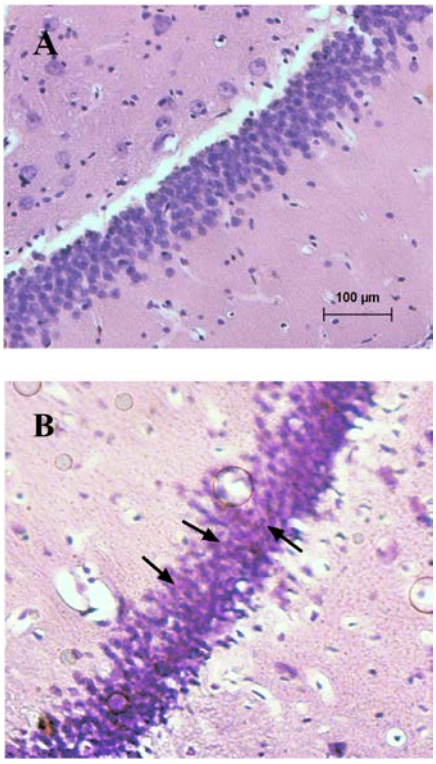

Fig. 3. Representative Aβ deposits in the hippocampal DG granule cells: (A) control and (B) Aβ (1-42). Congo red staining of slices showed Aβ deposits (red spots indicated by arrows) between DG granule cells in Aβ (1-42) group.

Discussion

The main finding of this study was that a single unilateral microinjection of nanomolar dose of aggregated form of Aβ (1-42) into the lateral ventricle significantly inhibited HFS-induced LTP in granular cells of the DG in hippocampus *in vivo*. Application of this peptide had no effect on baseline activity of granule cell layer's neurons but significantly decreased evoked field potential and this conclusion was supported by decreased fEPSP-LTP and PS-LTP in these neurons.

Our results were consistent with the previous studies which demonstrated that administration of Aβ reduces neuronal synaptic plasticity and LTP in the CA1 area of hippocampus (Freir *et al* 2001, Jing *et al* 2009). In addition, in vitro studies have shown that application of soluble form of Aβ (1-42) inhibited LTP in DG of hippocampal slices in Sprague-Dawley rats (Wang *et al* 2002), and in another research, a significant decrease in action potential generation was found with Aβ (1-42) in whole cell recording in hippocampal DG (Yun *et al* 2006).

The NMDA receptor-dependent LTP is the widely used form of synaptic plasticity that is generated by presynaptic release of glutamate and then depolarization of postsynaptic neuron that causes calcium influx by NMDA receptors. Elevation of cytoplasmic Ca^{2+} concentration results in an increased number of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) type of glutamate receptor (Bredt and Nicoll 2003). Reduction of glutamate receptor is one of the main synaptotoxic effects of Aβ. Previous studies have shown that Aβ can reduce the expression of NMDA receptors and administration of this peptide reduces the NMDA and AMPA receptor-mediated synaptic transmission by increasing endocytosis of these receptors (Snyder *et al* 2005, Hsieh *et al* 2006). On the other hand, activity-dependent autophosphorylation/activation of Ca^{2+} and calmodulin-dependent protein kinase II (CaMKII) and phosphorylation of GluR1 subunits of AMPA receptors at a CaMKII-dependent site were demonstrated along with generation of LTP in DG of hippocampal slices (Lisman *et al* 2002). Meanwhile, results of previous researches show that application of Aβ (1-42) inhibits NMDA receptor-mediated synaptic transmission resulting in reduced Ca^{2+} influx through the NMDA receptors and subsequently reduces the phosphorylation of CaMKII (Zhao *et al* 2004). According to these findings, in the present study, the attenuating effects of Aβ (1-42) on LTP in the granular cells of DG may be partly due to the elimination of glutamate receptors and reduced phosphorylation of CaMKII by this peptide.

Nevertheless, in contrast to our findings, results of some studies have demonstrated the Aβ-induced increase in synaptic currents and LTP. In a similar *in vivo* study, i.c.v. administration of aggregated Aβ significantly increased LTP in the CA1 area of hippocampus

(Trubetskaya *et al* 2003), and also in another *in vitro* research, Aβ at a low concentration enhanced LTP in hippocampal slices (Wu *et al* 1995b). These studies suggested that this increasing effect of Aβ on LTP might be related to augmentation of NMDA receptor-mediated synaptic currents and increase in intracellular Ca^{2+} concentration due to Aβ-induced oxidative stress.

Nicotinic acetylcholine receptors (nAChRs) in the brain are involved in learning and memory processes. Strong evidence has shown that Aβ peptides could produce cholinergic dysfunction and subsequently cognitive deficits in patients with AD (Tran *et al* 2002, Nordberg 2001). The α-7 nicotinic acetylcholine receptors (α7nAChRs) and α4,β2 nicotinic acetylcholine receptors (α4β2nAChRs) are two most abundant forms of nAChRs in the brain (Wu *et al* 2008). It is indicated that Aβ binds to α7nAChRs with high affinity and a close relationship is found between Aβ and α7nAChRs (Wang *et al* 2000). And it is shown that both of Aβ and α7nAChRs are present in amyloid plaques conformation in patients with AD (Dziewczapolski *et al* 2009). Previous studies have suggested that attachment of Aβ to α7nAChRs can initiate endocytosis of the complex of Aβ/α7nAChRs and consequently result in accumulation of intracellular Aβ and impairment of synaptic function (DAndrea and Nagele 2006). It is also proposed that α7nAChRs have a high permeability to Ca^{2+} and activation of these receptors by Aβ results in Ca^{2+} influx and overload of intracellular Ca^{2+} that is involved in Aβ-induced synaptic dysfunction (Brzyska and Elbaum 2003).

Moreover, presynaptic α7nAChRs, which are essential for learning and memory, are also decreased in AD. Aβ binds to these receptors and decreases the release of acetylcholine (ACh) as an excitatory neurotransmitter and impairs the long-term potentiation (Parri *et al* 2011, Walsh *et al* 2002).

Results of a study performed on hippocampal CA1 area in rat demonstrated that the α4β2nAChRs are required for suppressing action of Aβ on LTP. They suggested that Aβ may bind to α4β2nAChRs and activate these receptors on GABAergic inhibitory interneurons of CA1 region of hippocampus and consequently increase the inhibitory afferent to pyramidal cells that finally lead to reduced LTP in these neurons (Wu *et al* 2008). According to these findings, the impairing effects of aggregated Aβ (1-42) on LTP in our study might be partly due to such changes in nAChRs function in the synapses of granular cells of DG.

Conclusion

The present study indicates that administration of a single unilateral microinjection of aggregated form of Aβ (1-42) into the lateral ventricle effectively inhibits HFS-induced LTP in the granular cells of DG in hippocampus *in vivo*, presumably due to Aβ-induced elimination of glutamate receptors and reduced phosphorylation of CaMKII and also alteration in nAChRs function in the synapses of granular cells of DG.

Ethical issues

All stages of the present study were performed using protocols approved by the Research and Ethics Committee of Tabriz University of Medical Sciences and were conducted under the recommended conditions of Guide for the Care and Use of Laboratory Animals of National Institute of Health.

Competing interests

The authors declare no competing interests.

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