

## Lavandula angustifolia extract improves deteriorated synaptic plasticity in an animal model of Alzheimer's disease

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### ABSTRACT

**Objective(s):** Neurodegenerative Alzheimer's disease (AD) is associated with profound deficits in synaptic transmission and synaptic plasticity. Long-term potentiation (LTP), an experimental form of synaptic plasticity, is intensively examined in hippocampus. In this study we evaluated the effect of aqueous extract of lavender (*Lavandula angustifolia*) on induction of LTP in the CA1 area of hippocampus. In response to stimulation of the Schaffer collaterals the baseline or tetanized field extracellular postsynaptic potentials (fEPSPs) were recorded in the CA1 area.

**Materials and Methods:** The electrophysiological recordings were carried out in four groups of rats; two control groups including the vehicle (CON) and lavender (CE) treated rats and two Alzheimeric groups including the vehicle (ALZ) and lavender (AE) treated animals.

**Results:** The extract inefficiently affected the baseline responses in the four testing groups. While the fEPSPs displayed a considerable LTP in the CON animals, no potentiation was evident in the tetanized responses in the ALZ rats. The herbal medicine effectively restored LTP in the AE group and further potentiated fEPSPs in the CE group.

**Conclusion:** The positive effect of the lavender extract on the plasticity of synaptic transmission supports its previously reported behavioral effects on improvement of impaired spatial memory in the Alzheimeric animals.

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### Introduction

Alzheimer's disease (AD) is a common form of neurodegenerative disorder associated with progressive memory deficits (1, 2). Memory impairment, in particular the incapability to form and preserve new episodic memories, is characteristic of AD (3). AD is characterized by intracellular deposition of neurofibrillary tangles (NFTs) and extracellular deposition of amyloid  $\beta$ -protein ( $A\beta$ ) (4, 5).  $A\beta$  is generated through proteolysis of amyloid precursor protein (APP) by  $\beta$ -secretase and subsequently by  $\gamma$ -secretase (6). Hyperphosphorylation of tau proteins dissociates them from the microtubules and aggregates NFTs (7).

The hippocampus is crucial in memory storage and retrieval. The aggregated form of the  $A\beta$  initiates pathological processes in neurons of the hippocampus. In humans, the CA1 area of hippocampus is one of the first brain areas to display pathology of AD (8).

It is well known that long lasting changes in

synaptic efficacy is required for formation of learning and memory. Long-term potentiation (LTP), an experimental form of synaptic plasticity, has been proposed as a candidate mechanism of memory formation in hippocampal neural circuits. Description of cellular mechanisms of information storage is broadly described in the brain hippocampal LTP. Research indicates that an increase in the aggregated form of  $A\beta$  in senile plaques greatly diminishes LTP (9).

Acetylcholine is a neurotransmitter which is degraded by acetylcholinesterase (AChE), an enzyme that is considered to play a role in the pathology of AD. AChE is present in the brain and is detected in NFTs and neuritic plaques (10).

Inflammatory processes are among the candidate mechanisms involved in progression of AD. Several inflammatory mediators are increased in the brains of AD patients compared to age-matched controls, and many of these mediators have been localized to classical pathologic lesions in AD brains (11).

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The medicines currently available for AD are only able to delay the progression of the disease.

Lavender (*Lavandula angustifolia*) is a strongly aromatic sub-shrub at the Mediterranean region. Fresh flowers of this plant are mostly used for extract preparation. Numerous pharmacological effects including anticonvulsant, sedative, antispasmodic, analgesic, antioxidant and local anesthetic are attributed to lavender (12-14). This medicinal herb is found to be effective as an anticholinesterase and inhibitor of glutamate-induced neurotoxicity as well (15). Reports indicate that lavender extract is used in treatment of inflammation, depression, stress, and headache (16). We have previously demonstrated that lavender extract effectively underlies hippocampal related cognitive function (17). The present study was undertaken to evaluate the effect of the aqueous extract of the medicinal herb on LTP of synaptic transmission in the CA1 area of hippocampus of an animal model of Alzheimeric rat.

## Materials and Methods

### HPLC analysis

Twenty microliters of Lavender extract that was redissolved in methanol (10 mg/ml) was analyzed using an HPLC unit and a Spherisorb ODS2 column (4.6\*250 mm, 5  $\mu$ m particle size). The solvent system used was a gradient of water/formic acid (19:1) (A) and acetonitrile (B). the gradient was as follows: 0 min- 17% B; 40 min - 23% B; 57 min - 49% B; 59 min - 100% B; 60 min - 100% B. Elution was performed at a solvent flow rate of 1 ml/min. Detection was achieved with a Gilson diode array detector. The data were processed on a Uniport Software system; peak purity was checked using the software contrast facilities.

### Animals

Thirty two male Wistar rats weighing 250–300 g at the beginning of the experimental procedures were used. Rats were rendered Alzheimeric as described in the previous report (17). Briefly, the animals received an intracerebroventricular injection of 1 micrograms A $\beta$  1-42 (purchased from Sigma-Aldrich) via a Hamilton syringe. The experimental subjects were kept in a single holding cage and housed in a constant temperature of 21 $\pm$  2  $^{\circ}$ C and a humidity of 55 $\pm$  5% with free access to food and water *ad libitum*. All procedures were in accordance with the Guidelines of Ethical Committee, Deputy of Research, Kashan University of Medical Sciences, Kashan, Iran.

### Preparation of lavender extract

*L. angustifolia* was obtained from herbarium of Shahid Beheshti University of Medical Sciences, Tehran, Iran. For extraction, 250 g dried flowers of lavender was mixed with 1000 ml boiling water. The mixture was then stirred for 4 hr, filtered, and concentrated by

vaporizing. Lavender specimen was identified by Pharmaceutics Faculty of the university, where voucher specimens (1092) were kept. The extract was standardized based on 130 mg caffeic acid in each gram.

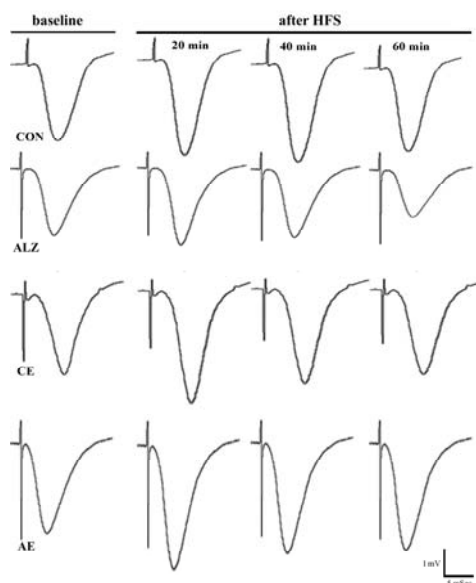
### Extract administration

The concentrated aqueous extract of lavender was suspended in distilled water. The control animals were intraperitoneally (IP) injected with either distilled water (CON) or 200 mg/kg of the lavender extract (CE). Also, Alzheimeric rats received distilled water (ALZ) or 200 mg/kg of the aqueous extract (AE). The administrations were carried out 20 days after A $\beta$  injection. The volume of injections was adjusted at 0.4 ml/kg body-weight for all groups of animals. The treatment was conducted once per day for 20 consecutive days prior to electrophysiological experiments.

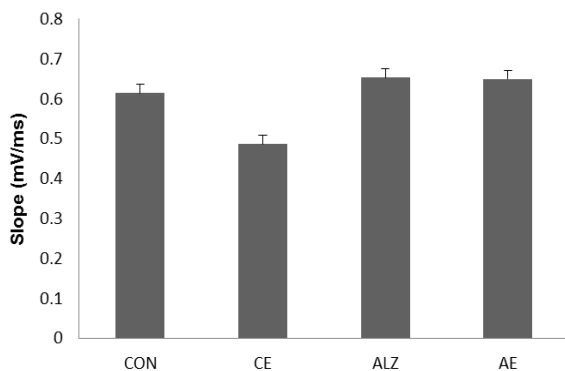
### Electrophysiology

#### Animal preparation and electrode implantation

The experimental subjects were anesthetized by urethane (1.5 g/kg, IP) and placed in a stereotaxic frame. Two holes were drilled above the skull with a sterile drill bit: a hole for the recording electrode (1 mm diameter, 4.2 mm posterior to bregma, 3.8 mm lateral to the midline) and another one for the stimulating electrode (1 mm diameter, 3.4 mm posterior to bregma, 2.5 mm lateral to the midline). All coordinates were based on the Stereotaxic atlas (18). The recording and stimulating electrodes were lowered into the CA1 stratum radiatum and the Schaffer collaterals, respectively. Extracellular recordings were referenced to an indifferent site on the skull.



**Figure 1.** Slope of the baseline and post-tetanus field potentials recorded in the CA1 area of hippocampus evoked by stimulation of the Schaffer collaterals



**Figure 2.** Representative traces illustrating the mean slope of the baseline responses and the changes in slope of the post-HFS fEPSPs over the first, the second and the third 20 min of recordings

### Hippocampal recordings

In response to test pulses applied to the Schaffer collaterals, evoked field extracellular postsynaptic potentials (fEPSPs) of the CA1 field were attained. The stimulus amplitude was determined by means of an input/output curve. The stimulation intensity was adjusted to a level that evoked a 60% of maximum fEPSPs for all phases of the experiment. The fEPSPs were recorded at 30 sec intervals for 30 min. Then, LTP was induced by high-frequency stimulation (HFS) of 100 Hz (10 bursts of 10 stimuli, 0.1 msec stimulus duration and 2 sec inter-burst interval). Following the tetanus, responses to the test pulses were collected continuously for 1 hr (Figure 1).

### Statistical analysis

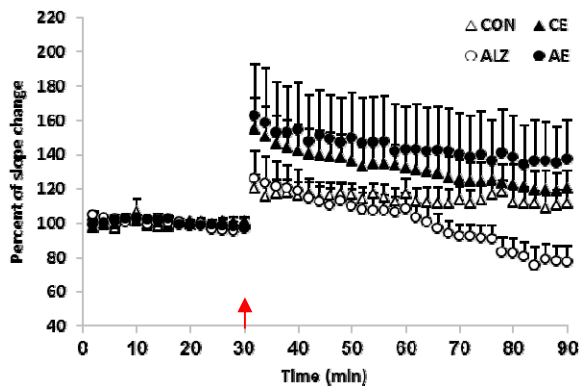
The data were considered for the pre and post-tetanic response changes. The slope of fEPSPs (millivolt/mili-sec) was considered for evaluation of recordings. The level of potentiation in the post-HFS responses was measured as:

$$\frac{\text{Post-tetanus value} - \text{Pre-tetanus mean}}{\text{Pre-tetanus mean}} * 100 + 100$$

Data are presented as mean±SEM and normalized by taking the pre-tetanus slope of fEPSPs as 100% and comparing the post-tetanus fEPSPs with it. The baseline and post-tetanus recordings of the four groups of animals were analyzed using two-way ANOVA followed by LSD posttest. The probability levels were interpreted as statistically significant if *P*-value was less than 0.05.

### Results

By stimulating the Schaffer's collaterals the baseline fEPSPs were recorded in the CA1 area of hippocampus. Then, the CA3-CA1 pathway was tetanized to assess the extent of post-HFS enhancement in the CA1



**Figure 3.** The percent of change in the slope of post-tetanus fEPSPs. While HFS considerably triggered LTP in post-tetanus responses, in the CON rats it failed to elicit a maintained potentiation in the fEPSPs in the ALZ animals. Lavender substantially lowered production of LTP in the AE group and further enhanced the synaptic plasticity in the CE group. Arrow indicates the time of application of the high frequency stimulation (HFS). Each point indicates data average obtained during 3 min

recordings. Analysis of variance indicated a significant general statistical difference between the data taken from the four groups of animals ( $F_{7,1342}=29.079, P<0.0001$ ).

### The baseline recordings in the CA1 area of hippocampus

Basic synaptic transmission was recorded in each group prior to application of the tetanic stimulation. Our results showed that A $\beta$  treatment at the dose of 1  $\mu$ g/2  $\mu$ l insignificantly influences the pre-tetanus field responses where the values in the CON and ALZ groups were 0.613±0.022 mV/ms and 0.652±0.023 mV/ms, respectively. Twenty day treatment of the animals with the lavender extract ineffectively affected the baseline fEPSPs in both CE and AE groups; values were 0.485±0.021 mV/ms and 0.649±0.021 mV/ms for the former and latter groups, respectively (Figure 2).

### Induction of LTP in the fEPSPs of the CA1 area of hippocampus

#### Occurrence of LTP in the CON animals

Tetanization of the Schaffer's collaterals resulted in a considerable LTP in the fEPSPs recorded in the CON group. Mean slope of post-tetanus responses increased more than 17% compared to the pre-tetanus recordings ( $P=0.001$ ). The potentiation was steadily observable as long as the recording continued.

#### Effect of the lavender extract on the induction of LTP in the CE animals

Administration of the herbal medicine effectively influenced the post-HFS enhancement in the CE rats, where the tetanic stimulation led to a further

**Table 1.** Values represent mean changes in the slopes of fEPSPs recorded in the four tested groups before and after tetanic stimulation

Mean slope of fEPSP Groups	Pre-tetanus (mV/ms)	Post-tetanus (mV/ms)	Approximate percent of potentiation
CON	0.613±0.022	0.72±0.022	17.3% P<0.0001
CE	0.485±0.021	0.588±0.013	21% P<0.0001
ALZ	0.652±0.023	0.67±0.023	2.7% P=0.841
AE	0.649±0.021	0.871±0.02	34.1% P<0.0001

P-values indicate the changes in slopes of the pre- and post-tetanus fEPSPs

potentiation in the fEPSPs ( $P=0.001$ ). The post-tetanus mean slope in this group increased by more than 21% and the potentiation lasted throughout the recording session. ANOVA indicated a significant variation ( $P<0.0001$ ) between the potentiated responses in the CON and CE groups. However, compared to the CON group, the LTP declined over recordings such that the degree of potentiation was almost similar in both CON and CE groups at the end of experiments.

#### Induction of LTP in the ALZ animals

Application of the tetanus failed to produce LTP in the ALZ group. The mean slope values of pre- and post-tetanus responses were  $0.652\pm 0.023$  mV/ms and  $0.670\pm 0.023$  mV/ms, respectively. Transient elevation of the fEPSPs slope immediately after HFS displayed a sharp decay so that the mean slope of recordings resembled that of the baseline responses about 30 min after the tetanic stimulation. The mean slope change percent was 2.7% indicating no difference between the pre- and post-tetanus responses slope ( $P=0.628$ ). Additionally, the post-HFS fEPSPs exhibited a real depotentiation when the recordings continued.

#### Effect of the lavender extract on the induction of LTP in the AE animals

Treatment of the Alzheimeric animals with the aqueous extract of lavender restored occurrence of LTP. HFS elicited a post-tetanus enhancement by 34.1% in the AE group ( $P<0.0001$ ). The statistical analysis showed a significant difference between the slope sizes of the post-HFS responses in the ALZ and AE animals ( $P<0.0001$ ). Figure 3 illustrates the post-tetanus changes in the vehicle and lavender treated control and Alzheimeric rats. Table 1 summarizes the changes in slopes of the pre- and post-HFS responses in the four testing groups.

#### Discussion

The neurodegenerative AD profoundly affects the cognitive functions of the brain (19). Attempts have been dedicated to prevention of the disease or overcoming its adverse effects (20). The present study was devoted to electrophysiological

assessment of synaptic transmission in the CA3-CA1 pathway, the well-known hippocampal neuronal circuit in memory consolidation. In this *in vivo* study the probable role of the lavender extract in the baseline as well as tetanized fEPSPs in the A $\beta$  injected animals was evaluated. We found that the baseline responses are not sensitive to the intraventricular injection of A $\beta$ , where the mean slope of fEPSPs was almost similar in both CON and ALZ groups. Consistently, Yamin reported that A $\beta$  strongly inhibits LTP in the fEPSPs of the CA1 area at doses that have no acute effect on baseline excitatory transmission (21).

On the other hand, whereas the tetanic stimulation elicited a considerable LTP in the fEPSPs in the CON animals, it failed to potentiate the responses in the A $\beta$  treated rats. These results are consistent with the report indicating that A $\beta$  pronouncedly prevents occurrence of LTP (22).

Administration of the lavender extract restored the induction of LTP in the AE animals, and additionally, led to a further potentiation in the CON rats. What are the probable mechanisms through which the herbal medicine improves the synaptic plasticity?

Research indicates that, in addition to LTP prevention, the A $\beta$  treatment results in impaired learning and memory. The neurotransmitter acetylcholine is crucial for memory, thinking and behavior. Involvement of cholinergic mechanisms in the biochemical and behavioral effects of soluble A $\beta$  has been demonstrated (23). There are evidences indicating that the inhibitory effect of A $\beta$  on LTP induction might be via inhibition of cholinergic transmission (24). Declined synthesis and/or release of acetylcholine are reported during treatment with A $\beta$  (25, 26). Also, Magdesian *et al.* reported the blockade of acetylcholine receptors under A $\beta$  administration (27). It is demonstrated that, through inhibiting AChE, lavender increases neurotransmitter activity in the brain. This may lead to increased availability of acetylcholine, which helps slow progression of AD symptoms including suppression of LTP induction (15).

It is reported that A $\beta$  may increase synaptic concentration of glutamate by inhibiting glutamate uptake or promoting the release of this

neurotransmitter (28). It may lead to a glutamatergic excitotoxicity, which is mediated by NMDA receptors (29). Consistently, it is shown that excessive release of glutamate plays an injurious role in ischemic injury of neurons (30). Also, evidence indicates that deficiencies in many stages of the glutamate cycle occurring in AD lead to increased synaptic concentrations of glutamate (31). It is found that aqueous extract of lavender flowers decreases glutamate induced neurotoxicity in rat pups' cerebellar granular cell culture (32). Additionally, antioxidant characteristics and AChE inhibition is reported for linalool; one of the main components in lavender oil. This indicates that several targets relevant to treatment of AD such as the cholinergic, neuroprotective and antioxidant activities could be found in lavender (33).

A $\beta$  induces secretion of pro-inflammatory molecules from microglia, and neuroinflammation is one of the key events in AD progress (34). In line, it is shown that intracerebroventricular injection of A $\beta$  stimulates secretion of inflammatory agents and, thus, is one of the main reasons of inflammation in Alzheimeric brains (35). Lavender is reported to be an efficient medicinal herb in treating inflammation (16). Anti-inflammatory activities of lavender have been reported for different extracts of Lamiaceae plants (36).

Altogether, the findings of the present study support the idea that the lavender extract positively underlies the NMDA receptor-mediated LTP in both the control and A $\beta$  treated animals (37).

## Conclusion

Our findings indicate that the herbal medicine extract is ineffective on basic synaptic activity in the hippocampal circuits; however, it has a positive impact on the tetanized NMDA receptor-mediated synaptic transmission in both the normal and specially the Alzheimeric animals.

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