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The Beneficial Effect of (-)-Epigallocatechin-3-Gallate in an Experimental Model of Alzheimer's disease in Rat: a Behavioral Analysis

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ABSTRACT

Background: Progressive cognitive decline is one of the hallmark symptoms of Alzheimer's disease (AD) which can be modeled by β-amyloid injection into specific regions of brain. Since epigallocatechin-3-gallate (EGCG) is a potent antioxidant agent which its role against oxidative stress and inflammation has been shown in prior studies, we tried to determine whether EGCG administration protects against β-amyloid-induced memory and coordination impairment in rats. **Methods:** Animals (male Wistar rats) were divided into four groups: sham operated, EGCG-pretreated sham operated (sham + EGCG), untreated lesion (lesion), and EGCG-pretreated lesion (lesion + EGCG). Animals in lesion, lesion + EGCG, and sham + EGCG groups received sterile saline or saline plus EGCG (10 mg/kg) intraperitoneally one day pre-surgery and every other day for three weeks. The lesion was induced one day after EGCG pretreatment by injection of 4 µl of sterile saline or water containing 2 nmol/µl β-amyloid (1-40) into the hippocampal fissure. For behavioral analysis, psychomotor coordination (PMC) index and spontaneous alternation behavior were assessed using Rota-rod Treadmill and Y-maze, respectively at the third week post-lesion. **Results:** We found that β-amyloid (1-40) injection into hippocampus can decrease these behavioral indexes in lesion group in comparison with sham group which is similar to behavioral changes in AD. On the other hand, pretreatment with EGCG can improve the PMC index and spatial Y-maze alternation in the lesion + EGCG group in comparison with lesion group. **Conclusion:** We concluded that EGCG can be effective in restoring β-amyloid-induced behavioral derangements in rats regarding coordination and memory abilities. *Iran. Biomed. J. 11 (4): 237-243, 2007*

Keywords: Alzheimer's disease (AD), Epigallocatechin gallate (EGCG), Hippocampus, Behavior

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1, 2]. The prevalence and incidence of AD have been shown to increase with age. The typical neuropathological changes in this degenerative disease were first described nearly one hundred years ago [3] by Alois Alzheimer in 1906 [3, 4]. The two major microscopically lesions are amyloid plaques and neurofibrillary tangles, which are found significantly more in AD than normal aging [5]. Among several pathogenic mechanisms for AD, it seems that inflammation, genetic factors [6] and oxidative stress [4] have more important roles. In addition, β-amyloid has been shown to induce oxidative stress as well, [5] through inducing the formation of unusually high concentration of oxygen and nitrogen-reactive species and a depletion of endogenous antioxidants that play a central role in damaging and killing neurons [4]. Increased oxidative stress and accumulation of oxidatively damaged nucleic acids, proteins, and lipids disrupt intracellular signal transduction systems and intercellular signaling molecules that are important for maintaining the cellular structure of the brain and its neuronal circuits and thus is thought to exacerbate brain aging and induce deficits in cognitive and psychomotor performance [7]. There are also increased levels of markers of oxidative

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stress in brain tissue from AD patients [4]. Neuronal degeneration and death in the neocortex and hippocampus are probably the causes of the impressive behavioral and functional deficits of patients with AD [8]. Clinical features of AD is characterized by gradually worsening memory in association with motor spatial skills (apraxia), language difficulties (aphasia, anomia), deficits in visual special skills (agnosia), and cognitive decline [2]. In addition, personality changes including decreased energy, indifference, impulsivity, or irritability are common early symptoms [3].

Although the search for a treatment for AD has not been successful [9], antioxidants showed beneficial effects in patients with AD, slowing the progression of disease [4]. In this respect, green tea contains many polyphenolic antioxidants and (-)-epigallo-catechin-3-gallate (EGCG) is the most powerful antioxidant responsible for anti-inflammation, neuroprotection, and cancer chemoprevention [10], antiangiogenic properties [11] and is a free radical scavenging substance [12]. Therefore, the present study was conducted to evaluate the beneficial effect of EGCG on behavioral abnormalities in an experimental model of AD in rat.

MATERIALS AND METHODS

Materials. Aβ-protein fragment (1-40) and (-)-epigallocatechin-3-gallate (EGCG) were purchased from Sigma Co. (USA). Aβ (1-40) was dissolved in deionized water at a concentration of 2 nmol/µl and then aliquot and stored at - 70° C before use. EGCG was dissolved in sterile normal saline immediately prior to use at final concentration of 5 mg/ml.

Animals. In this study, male Wistar rats weighing 240-300 g (Pasteur Institute of Iran, Tehran) were used. These animals were housed in laboratory cages and maintained on a 12-h light/dark cycle with free access to food and water throughout the study.

Experimental procedure. The animals (n = 24) were randomly divided into four groups: sham-operated, EGCG-pretreated sham-operated (sham + EGCG), untreated lesion (lesion), and EGCG-pretreated lesion (lesion + EGCG). In this respect, sham-operated group received 4 µl of sterile saline only once time by stereotaxic surgery into the hippocampal fissure and 0.5 ml of sterile saline intraperitoneally one day pre-surgery and continued every other day for 3 weeks. In addition, sham + EGCG group received 0.5 ml of (10 mg/kg) EGCG intraperitoneally and intra-hippocampal injection of 4 µl sterile saline. Lesion group received 0.5 ml of sterile saline intraperitoneally and intrahippocampal injection of (2 nmol/ µl) Aβ-protein fragment (1-40) in 4 µl water. Meanwhile, lesion+ EGCG group also received EGCG like sham + EGCG group and Aβ-protein fragment (1-40) like lesion group. Animals were anesthetized by intraperitoneal application of xylazine (20 mg/kg) and ketamine (100 mg/kg) and placed in a stereotaxic apparatus (Stoelting Co. USA). Unilateral lesion of the hippocampus (left side) was made by an injection of 4 µl of sterile saline or water containing Aβ-protein fragment (1-40) delivered by a 5 µl Hamilton syringe at the level of the hippocampal fissure at the stereotaxic coordinates used on the Paxinous and Watson atlas (1986): antero-posterior, -3.8 mm; lateral, 2 mm from bregma, and -3.5 mm ventral from skull surface with the incisor bar set at -3.3 mm. Injection was made during a 5-min period and then remained in place for 5 min before being slowly withdrawn (Fig. 1).

Behavioral tests. At the third week, post-lesion, behavioral tests were conducted on all animals (School of Medicine, Shahed University, Tehran, Iran).

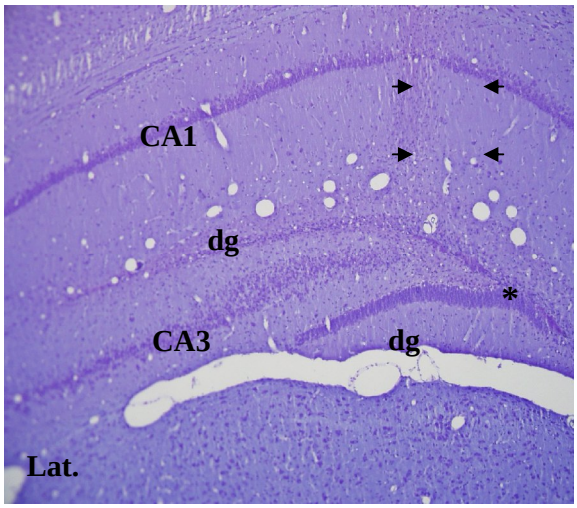


Fig. 1. The site of Aß injection in hippocampus in lesion group. The Figure shows that the Aß injection in the hippocampus can lead to degeneration of neurons in dentate gyrus. CA1 and CA3, fields of hippocampus; dg, dentate gyrus; *, depositions of Aß. Arrow heads show the site of injection. 100 ×.

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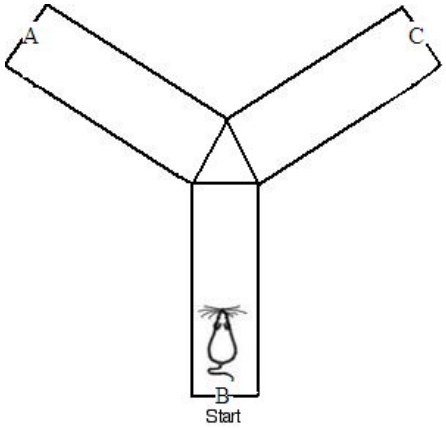


Fig. 2. A schematic figure of Y-maze box from above.

Spatial Y-maze memory. The experimental apparatus for Y-maze consisted of a black-painted maze made of Plexiglas. Each arm of the Y-maze was 40 cm long, 30 cm high and 15 cm wide [13] (Fig. 2) and positioned at an equal angle (labeled A, B and C) and converged in an equilateral triangular central area with 15 cm at its longest axis. The Y-maze can be used as a measure for short-term memory performance by recording spontaneous alternation behavior in a single session [13]. Each rat, naïve to the maze, was placed at the end of one arm and allowed to move freely through the maze during an 8-min session. The sequence of each arm entry recorded manually (i.e., ACBABACACBCAC AC, etc.). A spontaneous alternation behavior, which is regarded as a measure of spatial memory, was defined as the entry into all three arms on consecutive choices in overlapping triplet sets (i.e., ACB,ABA,CAC,BCA,CAC,) [13]. The percent spontaneous alternation behavior was calculated as the ratio of actual to possible alternations. Percent Alternation = [Actual Alternation (i.e., ACB, BCA = 6) / Maximum Alternation*(i.e., ACBABACACBC ACAC = 15 – 2 = 13)] × 100 = (6/13) × 100 = 46.15%. * Total Number of arms entered minus 2 [17]. Each test was done only one time on each animal.

Psychomotor coordination (PMC). This test was done by Rota-rod Treadmill with shock facility apparatus (Harvard model 865). The Rota-rod Treadmill is an established motor task for testing balance and coordination aspects of motor performance in rats [14, 15]. First, animals were trained by their placing on the rolling bar and had been to walk on it. Then, for 5 times, they were placed in the case with these characteristics: initial speed = 4 rpm, final speed = 30 rpm, initial to final speed time = 4 min, shock intensity = 1.1 mA, shock duration = 0.2-0.8 sec, experimental length time = 5 min, interval between experiments = 2 min. The mean stay time on the rod per trial was taken as a PMC index [8]. Also, the mean number of fallings for each animal was recorded. Each animal was experimented only one period in this test.

Statistical analyses. All data were expressed as mean ± SEM. The statistical test of one-way analysis of variance (ANOVA) was used for comparison among all groups and unpaired student t-test for each two groups. In all calculations, a difference at $p<0.05$ was regarded as significant.

RESULTS

All experimental animals well-tolerated surgical operation with no mortality until the end of the study. Body weight was measured before surgery and on the day of behavioral tests. There were no significant differences in body weight of animals before surgery and on the day of behavioral tests at the same time periods. Meanwhile, the body weight of all groups slightly and non-significantly increased on the day of behavioral tests as compared to data before surgery. Since differences in the results of behavioral tests were not statistically significant for sham-operated and sham + EGCG groups, therefore, the results of these two groups are presented as sham group only.

Spatial Y-maze memory. In this study, all experiments were conducted between 9 and 11 a.m. for all groups and only once for each animal. As Figures 3 shows, the mean scores of alternation behavior for sham, lesion, and lesion + EGCG groups were 84.4, 45.3, and 74.4, respectively. However, mean of alternation scores between all groups showed a significant difference ($p<0.0001$). There was also a significant decrease in this parameter in lesion group in comparison with sham group ($p<0.001$) and there was a difference between groups (lesion and lesion + EGCG groups) with a significant difference ($p<0.01$). Furthermore, there was no significant difference between sham and lesion + EGCG groups. On the other hand, as Figure 4 shows, there was no significant difference in the mean of total number of times the animals entered the arms(data were 16.7, 19, and 14.4 for sham, lesion, and lesion + EGCG groups, respectively).

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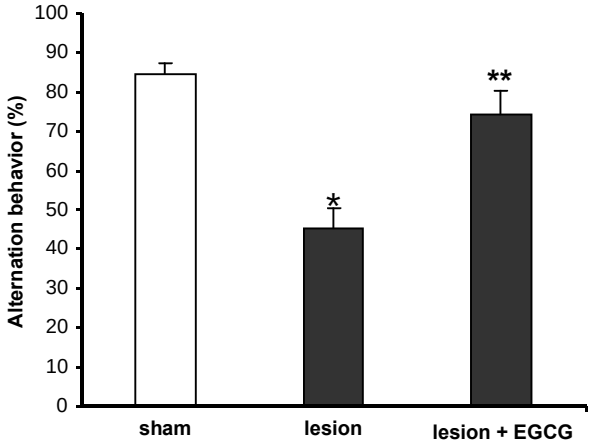


Fig. 3. Percent of Alternation behavior in Y-maze task on the third week post-lesion in studied groups (mean ± SEM). *p<0.001 as compared to sham group. **p<0.01 as compared to lesion group. Percent of alternation behavior = (Actual alternation/# maximum alternation) × 100. #Total Number of arms entered minus 2.

Psychomotor coordination (PMC). All experiments were carried out between 11 a.m. and 3 p.m. for all groups. As described above, we evaluated two parameters in this test, i.e., PMC index and mean number of fallings.

PMC index. Figure 5 shows the results of PMC test by Rota-rod Treadmill apparatus. This parameter exhibited a significant difference among all groups (p<0.001). The mean PMC indexes in all 5 times of experiments for sham, lesion, and lesion + EGCG groups were 158.5, 74, and 150.6, respectively.

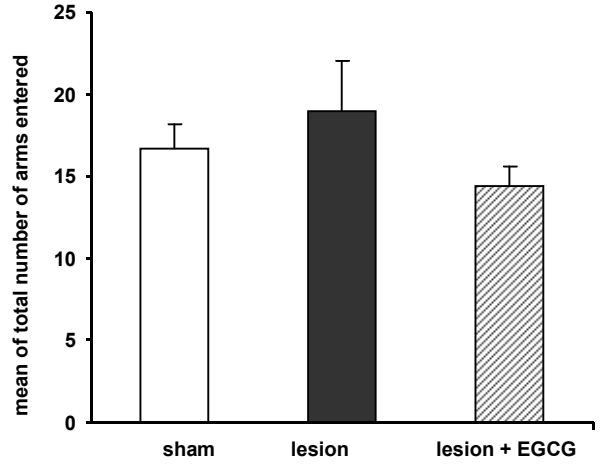


Fig. 4. Mean of total number of arms entered for Y-maze task in studied groups (mean ± SEM). There is no significant difference among groups.

Also, there were significant decreases of PMC index for lesion group in comparison with sham group (p<0.001) and with lesion + EGCG group (p<0.01). The mean PMC index for lesion + EGCG group also showed a non-significant decrease in comparison with sham group.

The number of fallings. Figure 6 shows the results of the mean number of animal fallings from the rod of the apparatus. This parameter exhibited a significant difference between all groups (p<0.05). The mean scores for sham, lesion, and lesion + EGCG groups were 68.1, 112.1, and 77.4, respectively. There were also significant increases in the mean number of fallings for lesion group in comparison with sham group (p<0.05) and also in lesion group with lesion + EGCG group (p<0.05). In addition, the mean number of fallings in lesion + EGCG group showed a non-significant increase in comparison with sham group.

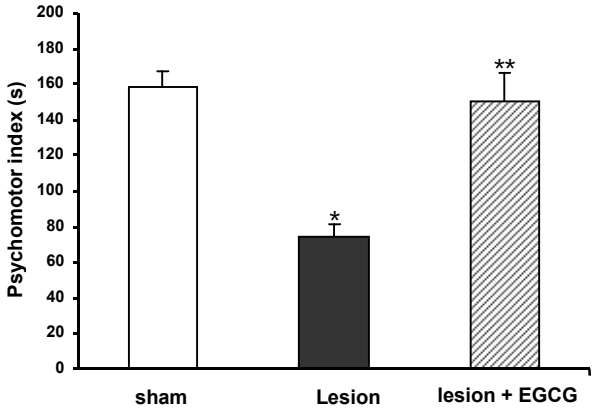


Fig. 5. Psychomotor coordination index by Rota-rod Treadmill apparatus in studied groups (mean ± SEM). *p<0.001 as compared to sham group; **p<0.01 as compared to lesion group.

DISCUSSION

The AD model as used in this research study showed that intrahippocampal injection of 4 µl of β-amyloid (2 nmol/µl) could induce deficits of behavioral indexes, which were evaluated by tests of PMC and spatial memory. PMC test showed that lesion group had a decrease in both psychomotor index and total number of fallings in comparison with other groups. In addition, related to the Y-maze test, lesion group showed decrease in alternation behavior scores in comparison with other groups.

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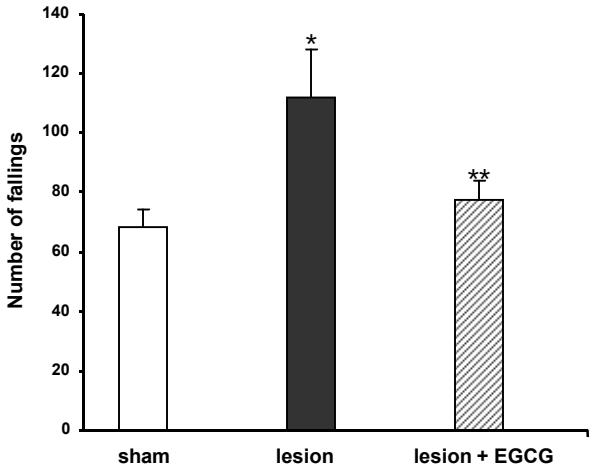


Fig. 6. Number of fallings in studied groups (mean ± SEM) by Rota-rod Treadmill apparatus. * $p<0.05$ as compared to sham group. ** $p<0.05$ as compared to lesion group.

There was not any significant change in the total number of times, the animals entered into the arms that it may be due to the good general condition of rats to move freely into the arms. Many investigators have reported that hippocampus is one of the most vulnerable regions in the AD brain [16] and hippocampal lesions in general produce changes in rat's activity levels [17] and impairment in spatial memory [18]. Although there are few reports on the behavioral effects of Aβ, recent researches showed intracranial injections of Aβ impair retention of active avoidance learning, Y-maze related memory ability, water-maze performance in mice or rats [9] and has toxic effects on brain cholinergic system [19]. Also, Aβ injection into hippocampus can deficit in both synaptic transmission and plasticity [20] and neuronal dysfunction [21]. In addition, several studies have reported that infusing Aβ peptide (1-40) into the rat cerebral ventricle induces learning impairment, neuronal and morphological degeneration and alteration of enzyme markers such as acetylcholine esterase and choline acyltransferase; all of which are well-known characteristics of AD [22]. Furthermore, Aβ peptide (1-40) injected into the hippocampus as well as the nucleus basalis can also impair learning and memory abilities in long term [19]. It seems that these impairments of behaviors in relation to learning and memory are due to the disturbance of the hippocampal circuit and its vast connections (through cortical and subcortical pathway) [23]. In the present study, it was shown that intraperitoneal injection of EGCG at a dose of 10 mg/kg administered one day pre-surgery and every other day for 3 weeks may prevent the changes of the psychomotor behavior and spatial memory against the decrease of their scores in the animal model of AD. Since these behavioral tests require the execution of complex coordinated movements and well-organized memory task in animal models of AD, therefore, behavioral improvement in this study may be attributed to the effect of EGCG on the sensorymotor capability and the power of memory in these animals [10]. Although, the mechanism of EGCG action is still unclear, EGCG has been found to inhibit cancer angiogenesis by suppressing vascular endothelial growth factor production [24]. EGCG have phenol rings that act as electron traps to scavenge peroxy radicals, superoxide anions, and hydroxyl radicals and prevent oxidation of iron. Therefore, we suggest that in addition to the reduction of iNOS expression, these compounds may block peroxynitrite and nitrite production through inhibition of oxidative reactions [25].

In addition, it seems that, EGCG may act as an antioxidant and anti-inflammatory agent [10] against β-amyloid aggregation in hippocampus and in this way EGCG may have a neuroprotective effect. Actually, Aβ neurotoxicity has been reported to be mediated by free radicals and attenuated by antioxidants and free radical scavengers [26]. EGCG has been shown to prevent Aβ−induced hippocampal neuronal cell death in cultured hippocampal neurons through its antioxidant property [27]. Intraperitoneal injection of EGCG in mutant amyloid precursor protein mice daily for 2 months indicated the reduced total Aβ levels [28]. Meanwhile, it has been found out that rats whose administered green tea catechins for 26 weeks had an improved reference and working memory-related learning ability [29].

In conclusion, the present results showed that unilateral intrahippocampal injection of 4 µl of 2 nmol/µl Aβ (1-40) can reduce the PMC and spatial memory in rats and intraperitoneal injection of 10 mg/kg of EGCG one day pre-surgery and every other day for 3 weeks may attenuate the induced changes of the PMC behavior and spatial memory by Aβ. Histological studies are warranted to clarify the real therapeutic and beneficial effects of EGCG.

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