Original Article

Effects of amitriptyline and fluoxetine on synaptic plasticity and TNF-α level at hippocampus of streptozotocin-induced diabetic rats

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Abstract

Introduction: Studies have indicated that diabetes mellitus impairs hippocampus. Diabetes increases the risk of depression and treatment with antidepressants may affect learning and memory. The aim of this study was to evaluate the effects of amitriptyline and fluoxetine on synaptic plasticity and TNF-α level in the hippocampus of streptozotocin-induced diabetic rats.

Methods: Experimental groups were control, diabetes, diabetes-amitriptyline and diabetes-fluoxetine (n=8 for each experimental group). Three weeks after the induction of diabetes, the rats received treatment with amitriptyline (5 mg/kg) or fluoxetine (5 mg/kg) for 21 days. Long-term potentiation (LTP) in perforant path-dentate gyrus synapses was assessed (by 400 Hz tetanization) for investigating the effect of treatments on synaptic plasticity. Field excitatory post-synaptic potential indices were measured. Finally, TNF-α levels were measured in hippocampus by enzyme-linked immunosorbant assay.

Results: Six weeks after the diabetes induction, LTP wasn't different between the control and the diabetes groups and also no significant differences were observed between the diabetes and the diabetes-treated groups; however, amitriptyline and fluoxetine impaired LTP in diabetic rats and there was a significant difference between the control and the diabetes-treated groups. Comparing to the controls, TNF-α level was increased significantly ($P<0.05$) only in the diabetes-amitriptyline group.

Conclusion: Results suggest that amitriptyline and fluoxetine intensify the destructive effects of diabetes on hippocampus and that TNF-α may act as a mediator for these changes; however, other factors may also be involved. Hence, treatment of diabetic patients with antidepressants must be done with extra care.

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Introduction

Diabetes mellitus (DM) is a chronic and progressive disease with a main sign of hyperglycemia. Diabetes, in addition to the environmental impacts, extensively damages the brain and causes cognitive disorders (Kodl and Seaquist, 2008). In the progression of

diabetes, the risk of depression increases which intensifies the pathogenesis of diabetes (Ho et al., 2013). One of the most important areas of the brain involved in cognitive function is the hippocampus and its damage plays a key role in depression (Sapolsky, 2001). It has been demonstrated that both survival and proliferation of hippocampal neurons are relatively lower in depressed than non-depressed diabetic patients (Ho et al., 2013). The function of the hippocampus is known to be seriously influenced by diabetes (Reisi et al., 2010b). Studies have shown that diabetes damages cell survival and proliferation (Zhang et al., 2008), synaptic transmission and plasticity in the hippocampus (Reisi et al., 2008), which may adversely affect learning and memory (Reisi et al., 2009a). One of the possible cellular mechanism underlying learning and memory is long-term potentiation (LTP) that is a form of activity-dependent synaptic plasticity (Bliss and Collingridge, 1993). It has been demonstrated that LTP is severely impaired in STZ-induced DM (Artola et al., 2005; Reisi et al., 2010b). These impairments initiate gradually from 6-8 weeks after the induction of diabetes (Kamal et al., 2000) and reach a maximum after 12 weeks (Biessels et al., 1996; Kamal et al., 1999). Thus, with regard to the relationship between diabetes and depression and their pathogenesis, a clearer understanding of the medication for depression in diabetes would be a necessity.

One of the common methods in the treatment of depression is the use of antidepressant. Studies have shown that these drugs affect the re-uptake of neurotransmitters, but other mechanisms maybe involved (Zarei et al., 2014). Amitriptyline and fluoxetine are two common antidepressants in which their neuroprotective, anti-inflammatory and antioxidant effects have also been observed (Yau et al., 2002; Wang et al., 2008; Kostadinov et al., 2014). It has been demonstrated that antidepressants reduce stress-induced atrophy of hippocampal cells and enhance hippocampal granular cells proliferation (Duman et al., 1999; Malberg et al., 2000). However, contradictory effects of these drugs have been reported. Studies showed that both fluoxetine and amitriptyline can decrease brain-derived neurotrophic factor (BDNF) (Xu et al., 2003; Khundakar and Zetterstrom, 2006) and treatment with these drugs impair learning and memory specially during short term treatments (Zarei et al., 2014).

Since diabetes is a chronic inflammatory disease and many of its central effects may be caused by inflammatory cytokines (Gaspar et al., 2016), the factors that affect the production and function of these cytokines may also lead to brain damage as a result of diabetes. Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine released from both neuronal and glial cells and is involved in processes such as neuroprotection and synaptic signaling, and has modulatory role on LTP in the hippocampus (Cumiskey et al., 2007; Wall et al., 2015). Therefore, the aim of this study was to investigate the effects of amitriptyline and fluoxetine on LTP induction and maintenance, which is a form of activity-dependent synaptic plasticity (Reisi et al., 2010b), and TNF-α levels in the hippocampus of streptozotocin-induced diabetic rats.

Materials and methods

Experimental animals
The experiments were carried out on male Wistar rats (280-300 g) that were housed under standard conditions of temperature (22 ± 2 °C) and light (12h light-dark cycle), with free access to food and water. The Ethic Committee for Animal Experiments at Isfahan University of Medical Sciences approved the study and all experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised in 1996.

Diabetes induction and treatments
The animals were randomly divided into four groups (n=8 in each group): the control, the diabetes, the diabetes-amitriptyline and the diabetes-fluoxetine groups. In the induction of diabetes, streptozotocin (Sigma Chemical Co, St Luis, MO, USA) was dissolved in saline and a single intraperitoneal (ip) injection of STZ (60 mg/kg) (Reisi et al., 2010a) was given to each animal. To confirm the induction of diabetes 3 days after the STZ injection, blood glucose levels (non-fasting blood glucose) were analyzed from blood samples obtained by tail prick using a strip-operated blood glucose monitoring system (Healthy Living, Samsung, Korea) and the animals with blood glucose levels higher than 300 mg/dl were selected (Reisi et al., 2010a).

Three weeks after the induction of diabetes, the rats

were treated with amitriptyline (5 mg/kg; Arasto Pharmaceutical Chemicals Inc.) or fluoxetine (5 mg/kg; Dr. ABIDI Pharmaceutical Laboratory) for 21 days (ip, dissolved in saline) (Zarei et al., 2014). Rats in the control groups received the same volume of saline.

Hippocampal electrophysiology

Twenty-four hours after the last treatment, the rats were anesthetized with urethane (1.8 g/kg, ip) and their heads were fixed in a stereotaxic head-holder. The skull was exposed and two small holes were drilled at the positions for 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 mmdiameter, Advent, UK) was placed in the perforant pathway (AP =−7.8 mm; ML= 3.5 mm; DV= 3.2-3.5 mm) and a stainless steel recording electrode was lowered into the dentate gyrus (DG) until the maximal response was observed (AP =−3.8 mm; ML= 2 mm; DV= 3.2–3.5 mm) (Paxinos, 2005). In order to ensure the minimization of trauma in the brain tissue, the electrodes were lowered very slowly (0.2 mm/min). Implantation of electrodes in the correct position was determined by physiological and stereotaxic indicators.

Extracellular evoked responses were obtained from the dentate granule cell population following the stimulation of the perforant pathway. Extracellular field potentials were amplified (1000✕) and filtered (1Hz to 3000Hz band pass). Signals were passed and analyzed through an analogue to digital interface (Electromodule D3111 and eProbe) provided by Science Beam Institute (Tehran, Iran). In order to evaluate synaptic potency, stimulus–response or input/output (I/O) functions was acquired by systematic variation of the stimulus current (100–1000µA) to ensure the evaluation of synaptic potency before induction of LTP. The population spike (PS) amplitude was measured as: [the difference in voltage between the peak of the first positive wave and the peak of the first negative deflection (VB − VC) + the difference in voltage between the peak of the second positive wave and the peak of the first negative deflection (VD − VC)]/2, and the field excitatory post-synaptic potential (fEPSP) slope was measured as the slope between the baseline and the peak of the first positive wave (AB slope) in order to
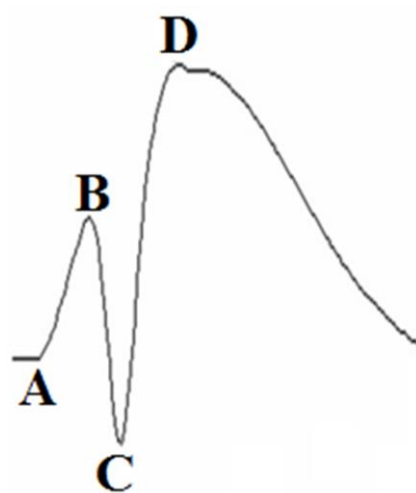

Fig.1. Schematic diagram of population spike (PS) and field excitatory post-synaptic potential (fEPSP) analysis. The PS parameters analyzed as: ([VB − VC] + [VD − VC])/2 (V: voltage) and fEPSP slope analyzed as: AB slope.

measure synaptic efficacy (Fig. 1).

The 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, 10s interburst interval) at a stimulus intensity that evoked a fEPSP of approximately 80% of the maximum response. All potentials used as baseline before and after high frequency stimuli were evoked at a stimulus intensity which produced 40% of the maximum response. The fEPSPs were recorded for the periods of 5, 15, 30 and 60 min after the high frequency stimuli in order to determine any changes in the synaptic response of DG neurons. For each time-point, 10 consecutive evoked responses were averaged at 10s stimulus interval (Reisi et al., 2010b).

Enzyme-linked immunosorbant assay (ELISA) for cytokine detection

The left hemisphere of the rat brain was dissected, and the hippocampus was immediately removed on a cold artificial CSF and stored at −80 °C. Tissues were homogenized with ice-cold 10 mM Tris-HCl buffer (pH 7.4). After centrifugation at 9,000 g for 30 min at 4 °C, the supernatant was collected for the measurement of total protein and TNF-α. Protein concentration was determined by a commercial protein assay, Bio-Rad

RC-DC Protein assay (Bio-Rad, UK), based on the traditional method of Lowry. The levels of TNF-α were measured by ELISA using Rat TNF-α Standard ELISA Development Kit (Peprotech, USA; Cat. No. 900-k73) (Azadbakht et al., 2015).

Statistical analysis

Data from LTP induction and maintenance were analyzed statistically using the two-way ANOVA and multivariate ANOVA, followed by LSD test. Hippocampal levels of TNF-α, blood sugar and body weight were analyzed using one-way ANOVA and Tukey for post-test. The significant level was set at $P<0.05$. Results are expressed as mean ± SEM.

Results

The body weights of diabetes and diabetes treated rats were significantly lower than that of the control group ($P<0.001$; Fig. 2). The blood glucose concentrations of these diabetic rats increased significantly comparing to the controls ($P<0.001$; Fig. 3).

As it is shown in Figure 4, the effects of treatment with amitriptyline and fluoxetine on LTP induction and maintenance in DG of diabetic rats were determined. Test of within-subject effect showed a reduction in the LTP maintenance across the progression of time at PS (TIME effect, $F_{(3,84)}=2.66$, $P=0.053$; Fig. 4A) and at slope (TIME effect, $F_{(3,84)}=3.147$, $P=0.029$; Fig. 4B). Also, it showed that the pattern of reduction was same between the groups as seen at PS (TIME & TREATMENT effect, $F_{(9,84)}=1.59$, $P=0.13$; Fig. 4A) and at slope (TIME & TREATMENT effect, $F_{(9,84)}=1.77$, $P=0.085$; Fig. 4B).
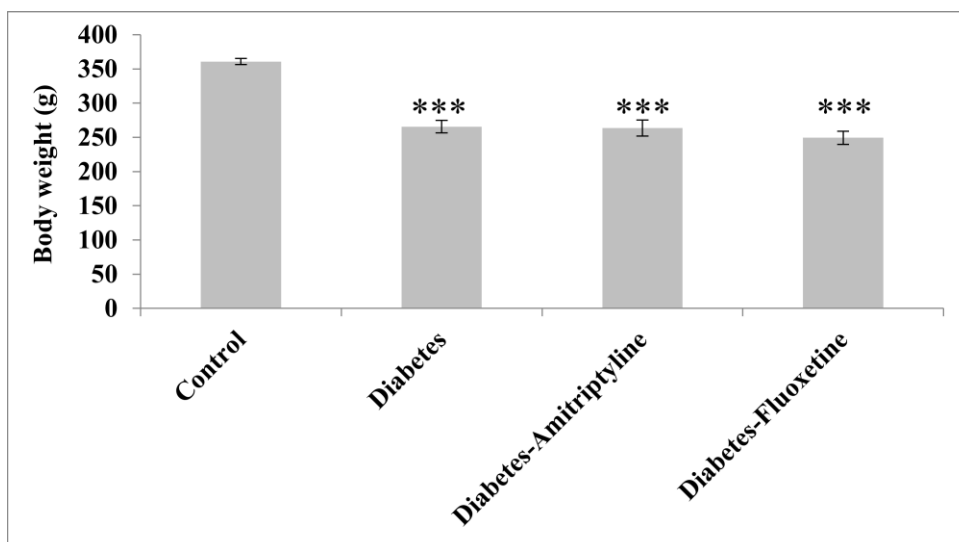

Fig.2. Effect of diabetes and treatment with amitriptyline (5 mg/kg) and fluoxetine (5 mg/kg) on mean body weight (g±SEM). ****P*<0.001 with respect to the control group (n=8 for each experimental group).

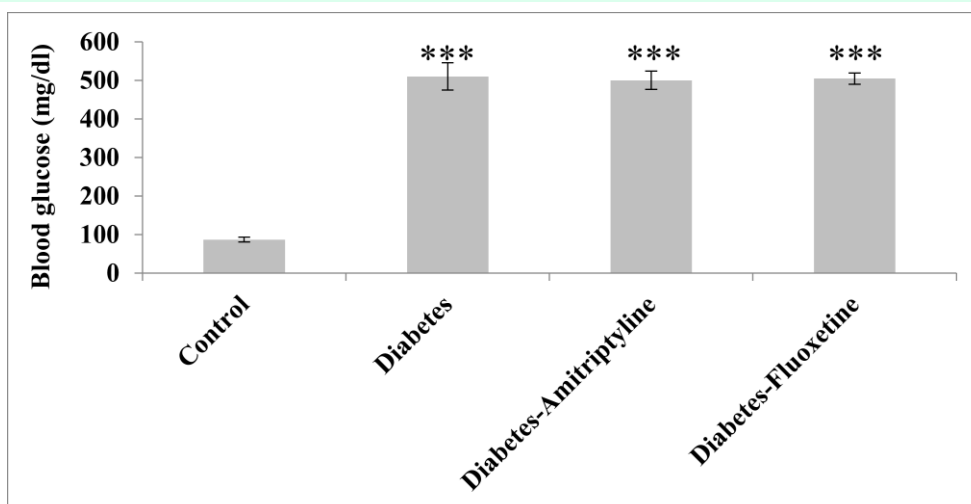**Fig.3.** Effect of diabetes and treatment with amitriptyline (5 mg/kg) and fluoxetine (5 mg/kg) on mean blood glucose concentrations (mg/dl±SEM). ****P*<0.001 with respect to the control group (n=8 for each experimental group).
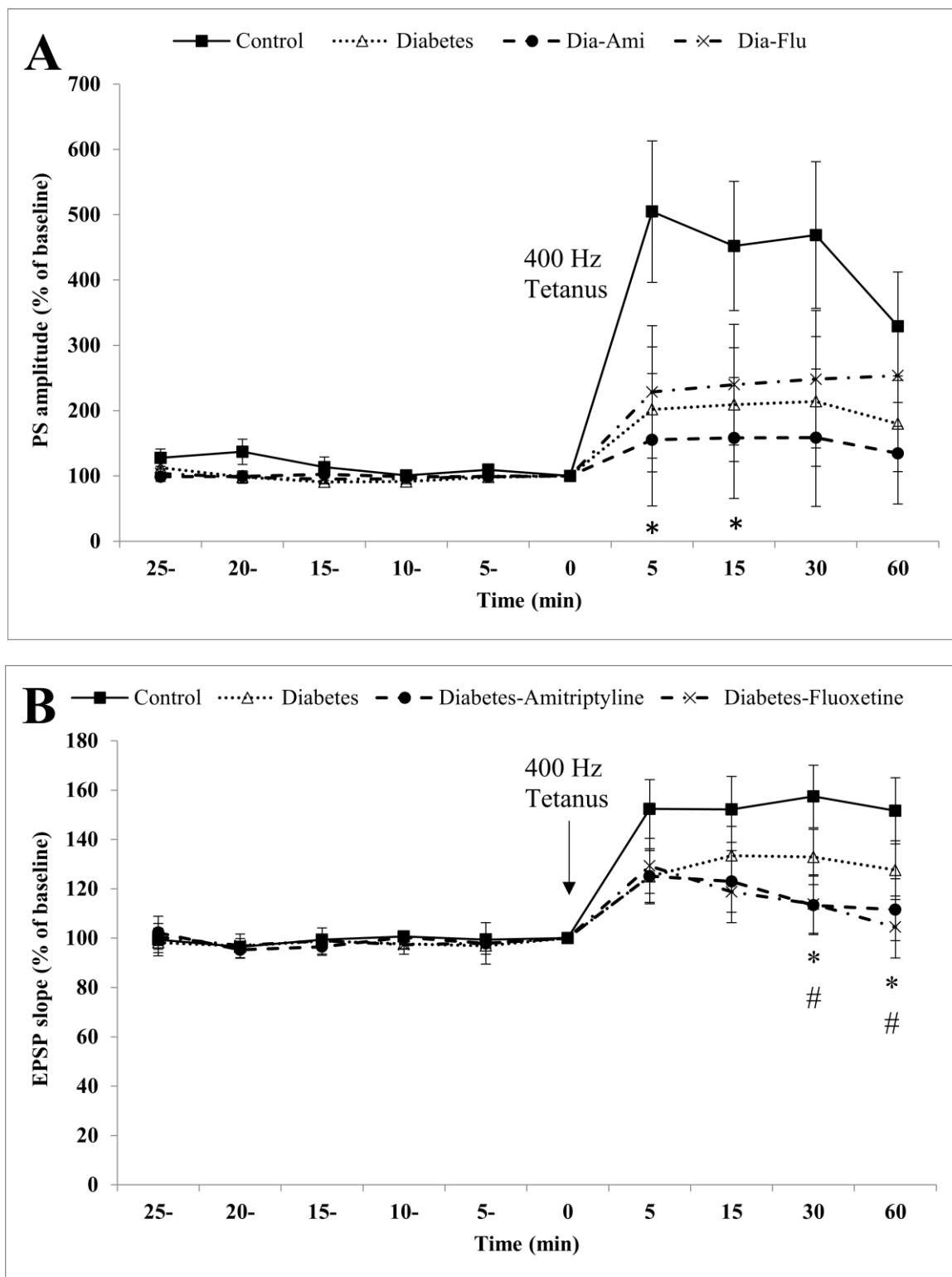
Fig.4. Effect of diabetes and treatment with amitriptyline (5 mg/kg) and fluoxetine (5 mg/kg) on LTP induction and maintenance in dentate gyrus of the hippocampus using 400 Hz tetanic stimulation at: (A) The magnitude of population spike-LTP and (B) field excitatory post-synaptic potential slope-LTP. Data are plotted as the average percentage change from baseline responses. Values are % mean±SEM. *$P<0.05$, significant difference between diabetes-amitriptyline and control groups; #$P<0.05$, significant difference between diabetes-fluoxetine and control groups (n=8 in each group).

Between group comparisons indicated that fEPSP-LTP after tetanization did not show any significant difference among the diabetes and the control groups at PS (201.31±86.33% and 438.72±97%,

respectively; P=0.08; Fig. 4A) and slope (129.8±10.7% and 153.42±12.1, respectively; P=0.155; Fig. 4B).

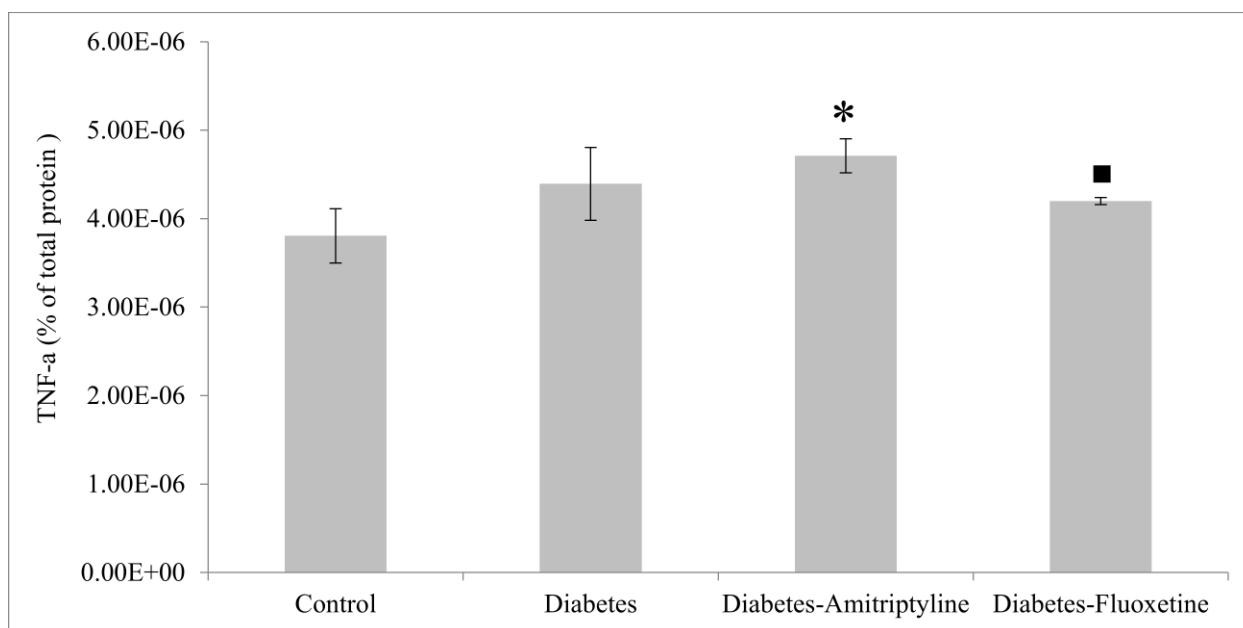With regard to the control group, PS decreased

Fig.5. Effects of treatment with amitriptyline (5 mg/kg) and fluoxetine (5 mg/kg) on ratio of TNF-α to total protein (%) in the hippocampus. Data are expressed as mean±SEM (n=8). *$P<0.05$ with respect to the control group, ■$P<0.05$ with respect to the diabetes-amitriptyline.

significantly in the diabetes-amitriptyline group (151.69±91.57%; P=0.041; Fig. 4A), but this situation was absent in the diabetes-fluoxetine group (242.56±91.57%; P=0.15; Fig. 4A). The slope was decreased significantly in both the diabetes-amitriptyline (118.2±11.36%; P=0.044; Fig. 4B) and diabetes-fluoxetine (116.6±11.36%; P=0.035; Fig. 4B) groups with respect to the control group.

The diabetes-amitriptyline and the diabetes-fluoxetine had no significant differences with respect to the diabetes group at PS (P=0.69 and P=0.74, respectively). Also, there were no significant differences at slope of the diabetes-amitriptyline (P=0.46) and the diabetes-fluoxetine (P=0.4) groups comparing to the diabetes group.

As shown in Figure 5, diabetes and its treatment with fluoxetine, in diabetic rats had no significant effects on the ratio of TNF-α level to the total protein content in the hippocampus compared to the control group. However, amitriptyline significantly ($P<0.05$) increased that ratio with respect to control group. There is a significant difference between the diabetes-amitriptyline and diabetes-fluoxetine groups ($P<0.05$).

Discussion

The results showed that a 6 week-post diabetes induction did not result in a corresponding change in hippocampal TNF-α levels and had no significant effects on long term potentiation in the DG following the electrical stimulation of the perforant pathway in rats.

It has been established that diabetes can decrease LTP or leave it unaffected (Belanger et al., 2004; Artola, 2013). It has been suggested that these changes are associated with alteration in NMDA and AMPA receptors levels, or both (Sasaki-Hamada et al., 2012). Inconsistent results according to the changes of synaptic transmission have been reported (Artola, 2013). These contradictory results may depend on the time of measurement of synaptic plasticity following the induction of diabetes. Previous studies have confirmed the impairment of synaptic plasticity as a result of diabetes gradually after 6-8 weeks and this may reach its maximum after 12 weeks (Reisi et al., 2008). Seemingly, an optimum time was not allowed for significant impairment of LTP in this present study.

Remarkably, amitriptyline and fluoxetine could damage LTP induction and the maintenance in hippocampus of diabetic rats, although the devastating effects of amitriptyline were more pronounce. Although some studies have shown favorable effects of antidepressants, in contrast to our results, undesirable effects are also observed (Zarei et al., 2014). A significant proportion of diabetic patients have depressive disorder and studies have

raised the bilateral relationship between depression and diabetes. In addition, many studies have shown the role of inflammation as the missing link between diabetes and depression (Laake et al., 2014). Antidepressants such as fluoxetine and amitriptyline, in addition to its positive effects in the treatment of depressive disorders, were analyzed due to their anti-inflammatory effects (Kostadinov et al., 2014). However, in this study, both of these antidepressants damaged hippocampal synaptic plasticity.

Studies have substantially reported that diabetes alters the levels of TNF-α, and TNF-α has paradoxical effects in the pathogenesis of diabetes, which may set in with time (Chee et al., 2011). TNF-α are produced by some neurons, microglia and astrocytes in the brain (Loane and Byrnes, 2010). TNF-α has neuromodulatory effects in the brain and regulates many cognitive activities (McAfoose and Baune, 2009). It has been shown that TNF-α levels were high during the onset of diabetes and then reduced thereafter (Christen et al., 2001). The levels of TNF-α in the hippocampus were found to be unchanged in the diabetes and diabetes-fluoxetine groups, but it increased in the diabetes-amitriptyline group. Studies have reported conflicting results concerning this reduction (Campelo et al., 2011) or enhancement of TNF-α (Hinze-Selch et al., 2000) following the use of amitriptyline. These contradictory effects may be time-dependent, because amitriptyline increases TNF-α initially and then decreases it (Renauld et al., 2004; Reynolds et al., 2004). It has been confirmed that fluoxetine decreased TNF-α levels in the models of diabetes (Habib et al., 2015); however, other studies have suggested that enhancement of TNF-α is a part of its mechanism for the treatment of depression (Warner-Schmidt et al., 2011; Duseja et al., 2015).

Our results showed that amitriptyline damaged LTP more than fluoxetine did. Since amitriptyline enhanced the level of TNF-α in hippocampus, the impairment of LTP may be partly related to this cytokine. Many studies have suggested that TNF-α damages neuronal plasticity (Curran and O'Connor, 2001), but recent studies have shown that enhancement of TNF-α produces therapeutic effects in the brain (Duseja et al., 2015). In this study, fluoxetine impaired LTP too, but TNF-α was unchanged in the diabetes-fluoxetine group. Therefore, other mechanisms may also be involved

for impairments of synaptic plasticity in diabetic rats following the administration of these antidepressants. Both diabetes and amitriptyline have been shown to increase apoptosis in the central nervous system (CNS) (Zschocke et al., 2011; Kahya et al., 2017). Amitriptyline neurotoxicity have been reported by a large number of studies. Amitriptyline directly causes mitochondrial respiratory chain dysfunction and may lead to an increase in reactive oxygen species and oxidative stress in cells (Lee et al., 2015). Hence, the effect of diabetes by the creation of oxidative stress in neurons (Kahya et al., 2017) and the potentially damaging effects of amitriptyline can together strengthen neuronal apoptosis and reduce LTP. Studies have shown contradictory effects of amitriptyline and fluoxetine on BDNF and many of such studies have observed a reduction in BDNF following the administration of these two antidepressants (Xu et al., 2003; Khundakar and Zetterstrom, 2006).

Since anticholinergics induces memory impairment (Campbell and Macqueen, 2004), amitriptyline can also cause the impairment of learning and memory through its strong anticholinergic effects (Brunnauer et al., 2006).

Studies have shown that fluoxetine can impair synaptic transmission via affecting synapse formation, presynaptic calcium voltage channels and postsynaptic acetyl choline receptors (Getz et al., 2011). Also, fluoxetine could lead to the activation of apoptotic pathways (Djordjevic et al., 2012) and damage neuronal growth (Xu et al., 2010). These damages can be aggravated by the onset of diabete and create a more serious injury in the CNS. Additionally, diabetes by enhancement of plasma corticosterone levels, causes a dysfunction of 5-hydroxytryptamine receptors and can affect the action of fluoxetine (Miyata et al., 2004). GABAergic system which has a significant role in the hippocampal synaptic plasticity (Reisi et al., 2008), has been suggested to be impaired both by diabetes (Reisi et al., 2009b) and fluoxetine (Caiati and Cherubini, 2013; Duarte, 2015). Besides, fluoxetine has been demonstrated to induce hyponatremia (Strachan and Shepherd, 1998), therefore fluoxetine possibly can worsen electrolyte imbalance caused by diabetes (Liamis et al., 2014) and precipitate diabetes complications. Both amitriptyline and fluoxetine can also increase blood sugar levels, which may lead

worsen diabetic conditions (Gomez et al., 2001; Chadwick et al., 2007; Mahmood et al., 2010).

Conclusion

In this study, fluoxetine and amitriptyline were observed to have deleterious effects on hippocampal LTP induction and its maintenance in diabetic rats. Following three weeks post-treatment, it seems that these antidepressants exacerbate diabetic effects in inducing memory impairment. Although enhancement of TNF-α in the hippocampus following the administration of amitriptyline can be an important factor, other factors must also be considered because fluoxetine could deteriorate diabetic effects without affecting the hippocampal TNF-α. To better understand the effects, further studies are needed, especially for the long-term effects of these drugs. Anyway, prescription of antidepressants should be done with extra care in diabetic patients especially during the first days.

Acknowledgments

Conflict of interest

The authors declare that they don't have any conflict of interest.

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