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Original Article

Therapeutic effects of exercise, escitalopram and exercise-accompanied escitalopram on brain functions in rats with depression

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ABSTRACT

Introduction: Depression impairs brain functions and memory processes. In a state of depression, escitalopram (as an antidepressant drug) and exercise (as an alternative lifestyle) both affect brain functions. Therefore, this study compared the therapeutic effects of exercise, using escitalopram at two different doses and exercise-accompanied escitalopram on different aspects of brain functions in rats with depression.

Methods: Male rats were randomly allocated into nine different groups of control, sham, depression, depression-rest, depression-exercise, depression-escitalopram 10, depression-escitalopram 20, depression-escitalopram 10-exercise and depression-escitalopram 20-exercise. Chronic restraint stress (6h/day, 14 days) was applied to induce depression. The escitalopram injections and treadmill running (1h/day, 14 days) were performed after the stress-induced depression. Moreover, different aspects of brain functions like learning, memory, memory consolidation and locomotor activity were evaluated via the passive avoidance test.

Results: The results indicated that depression disrupted learning, memory and memory consolidation. Escitalopram at a dose of 20mg/kg, exercise-accompanied escitalopram 20mg/kg and only exercise improved them significantly. In rats with depression, escitalopram at a dose of 10mg/kg (with and without exercise) enhanced memory in depression non-significantly. Moreover, the locomotor activity was decreased in groups with exercise-accompanied escitalopram 20mg/kg and exercise compared to only allowing a rest period after depression.

Conclusion: Overall, escitalopram 20mg/kg, exercise-accompanied escitalopram 20mg/kg and only exercise had therapeutic effects on memory improvement in subjects with depression. Since the combination of escitalopram 20mg/kg and exercise had a partial additive effect, it was the best treatment protocol for reversing the memory deficits in rats with depression.

Keywords:
Escitalopram
Exercise
Depression
Chronic stress
Memory
Locomotor activity

Introduction

According to previous studies, almost 15% of the world's population has been affected by depression at least once in a lifetime. Depression is seen to be the second most common cause underlying many global diseases nowadays that may lead to other disorders such as cognitive impairment (Dillon and Pizzagalli, 2018; World Health Organization 2016). As such, stressful

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events in life are also important risk factors for the induction of depression (Mahar et al., 2014). Stress and depression-induced conditions affect brain functions including learning and memory (Dillon and Pizzagalli, 2018; Mahar et al., 2014) though different mechanisms, such as changes in neural plasticity, neurotransmitter secretion and the involved receptor subtypes (Liu et al., 2017; Nemeroff, 2002). Nevertheless, the depression mechanisms and depression-related disorders have not been fully described yet. For instance, the reduction of serotonin is indicated as a key role in the pathophysiology of depression (Daut and Fonken, 2019; Kraus et al., 2017; Mahar et al., 2014). However, certain types of depression-related disorders need complementary medicine and/or alternative treatments (Thachil et al., 2007).

Over the past few decades, different methods have been utilized for the treatment of depression, including the use of chemical antidepressants and herbal plant drugs, as well as changes in lifestyle like doing exercise and changing nutrition. All of these changes have displayed some positive effects on memory disorders (Couto et al., 2012; Motaghinejad et al., 2015; Sun et al., 2013). Among different factors that are involved in brain functions, it is confirmed that serotonin is an important neurotransmitter with a key role in depression, moods, emotions, learning and memory homeostasis (Cowen and Sherwood, 2013; Mahar et al., 2014). Moreover, it has downstream effects on two important memory-associated neurotransmitters containing GABAergic and glutamatergic neurons (Marsman et al., 2017; Myhrer, 2003); that is because these neurons express various serotonin receptor subtypes as well (Martín-Ruiz et al., 2001; Santana et al., 2004). Therefore, not only serotonin plays a key role in memory, but also it regulates other neurotransmitters that are involved in memory. Hence, selective serotonin reuptake inhibitors (SSRIs) are often indicated as the first-line antidepressant treatments because of their relatively low side effects, good tolerability and the low risk of drug overdose/toxicity (Nemeroff and Owens, 2004). However, escitalopram, which is the *S*(+)-stereoisomer of the racemic compound citalopram, was therapeutically determined as one of the best SSRI antidepressant drugs. It acts on the primary serotonin transporters and the allosteric serotonin transporter sites (Zhong et al., 2012). It has been shown that escitalopram could significantly improve different types of memory in subjects with depression (Soczynska et al., 2014). Since depression has persistently been at high recurrent rates, SSRIs only affected one-third of the patients in remission (Rush et al., 2009).

Conversely, exercise is a subset of planned, structured and repetitive physical activities with a final or intermediate objective of improving or maintaining health (Caspersen et al., 1985). Some studies have confirmed the beneficial effects of exercise on neurogenesis, neuroanatomical system, learning and memory (Chang et al., 2012; Cox et al., 2016; Van Praag, 2008; Vivar et al., 2012). Moreover, it is reported that doing exercise exerts potent antidepressant effects (Josefsson et al., 2014; Lapmanee et al., 2013). Hence, it is indicated as one of the useful treatment methods to alleviate depression and cognitive impairments (Motaghinejad et al., 2015). Notably, regulating the secretion of neurotransmitters, especially serotonin, influences the impact of exercise on brain functions (Lin and Kuo, 2013). Therefore, it is proposed that exercise inhibits the serotonin reuptake by increasing both stimulatory activity of serotonin neurons and inhibition of serotonin reuptake in the serotonin-releasing neurons (Dremencov et al., 2017). In addition, medications cause side effects on the physiological system at different levels. Hence, exercise might help the improvement of the brain functions while administering less medications.

As such, the prevalence of stress and depression in today's societies can lead to impaired memory. Also, not receiving full treatment for the memory impairments (due to using antidepressants), increases the probability of recurrent depression periods. Even though, based on findings from previous studies, escitalopram and exercise each affected brain functions via serotonin secretion (Lin and Kuo, 2013; Zhong et al., 2012). Therefore, it is concluded that exercise can be a promising non-pharmacological treatment strategy for depression-induced memory impairments. That is because exercise may assist antidepressants to affect brain functions. Furthermore, despite the available literature on the impact of escitalopram and exercise alone on depression and its relevant disorders, there is no published report on the comparative therapeutic effects of escitalopram, exercise and exercise-accompanied escitalopram on brain functions yet. The effects of different doses of escitalopram on brain functions are discussed before. Therefore, this study aims to compare the therapeutic roles of two doses of escitalopram (10 and 20mg/kg/day), exercise

and escitalopram-accompanied exercise on different aspects of brain functions, such as learning, memory, memory consolidation and locomotor activity in rats with chronically stress-induced depression.

Materials and methods

Seventy-two male Wistar rats (with weights of 200–250g) were obtained from the animal nest in the Faculty of Pharmacy at the Isfahan University of Medical Sciences. The Ethics Committee of Animal Use at this University approved the study procedures (IR.MUI.MED.REC.1398.606). Accordingly, all experiments were conducted in compliance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No.80-23 ; revised 2011).

Every four rats were housed in a cage under standard conditions with a 12h light/dark cycle (lights on from 07:00 to 19:00) and a constant temperature of 23±2°C. Food and water were made available *ad libitum*. Also, animals received a 2-week adaptation period. The behavioral experiments were performed between 14:00 and 16:00. Eventually, the animals were randomly assigned to nine different groups (n=8 in each group) as follows:

1) The control (Co) group, in which the rats were transferred to the laboratory and received no special treatments; 2) sham (Sh) group, in which the rats were placed on the off treadmill 1h/day for the next 14 days; 3) depression (Dep) group, in which the rats were exposed to continuous restraint stress 6h/day for two consecutive 14-day periods (overall, 28 days); 4) depression-rest (Dep-Rest) group, in which the rats were first exposed to restraint stress 6h/day for 14 days and then were kept in their cage without any special treatment for the next 14 days; 5) depression-exercise (Dep-Exe) group, in which the rats were exposed to restraint stress for 6h/day for 14 days and then received 1h/day regular exercise for the next 14 days; 6) depression-escitalopram10 (Dep-Esc10) group, in which the rats were exposed to restraint stress 6h/day for 14 days and then received 10mg/kg/day escitalopram for the next 14 days; 7) depression-escitalopram20 (Dep-Esc20) group, in which the rats were exposed to restraint stress 6h/day for 14 days and received 20mg/kg/day escitalopram for the next 14 days; 8) depression-escitalopram-10-exercise (Dep-Esc10-Exe) group, in which the rats were exposed to restraint stress 6h/day for 14 days and then received 10mg/kg/day escitalopram and regular exercise for the next 14 days; 9) depression-escitalopram-20-exercise (Dep-Esc20-Exe) group, in which the rats were exposed to restraint stress 6h/day for 14 days and then received 20mg/kg/day escitalopram and regular exercise for the next 14 days.

Stress paradigms

Even though a similar study had reported the restraint stress-induced depression was indicated by a daily duration of 2.5h for 14 days (García-Rojo et al., 2017), to induce depression in this study, the rats were placed in Plexiglas restrainers for 6h/day (between 8:00–14:00) during 14 days. On day 14, after verifying the depression induction via forced swim test, the depressed rats were moved to the experimental protocol. An increase in the immobility time was considered as a sign for the correct induction of depression (García-Rojo et al., 2017). Notably, 6h/day of restraint stress for 14 days had a success rate of 80% in inducing depression-associated memory impairments in this study.

Drugs

The animals in depression received intraperitoneal injections of pure escitalopram oxalate powder (at doses of 10 and 20mg/kg; Sobhan-Daru Co., Iran), dissolved in the sterile normal saline (0.9%) for 14 consecutive days (Jastrzębska et al., 2017).

Exercise protocol

All rats in the exercised groups ran on the rodent treadmill every day (Maze router., Tabriz, Iran). The animals were previously familiarized with the treadmill running 3 days before the experiments. The exercise protocol consisted of running at a slope of 0º and 20–21 m/min, 1h/day for 14 consecutive days. The rats were forced to run at the speed of the treadmill by receiving a mild electric shock (about 0.3mA) from the grid behind the treadmill. The electric shocks were used sparingly to promote running. After the warm-up, the running intensity was kept at a constant speed/duration rate of 20m/min and 1h per run during the whole exercise.

Behavioral paradigms

In this study, different aspects of brain functions, such as learning, memory, memory consolidation and locomotor activity were measured by the passive avoidance

test as a behavioral task. The passive avoidance apparatus (64×25×35cm) was divided into two compartments of the same size with grid floors that were separated by a sliding guillotine door.

On Day 26 of the experiment, each rat was placed in the apparatus for a duration of 300s to be habituated. A single learning trial was performed on the following day (day 27). In the learning trial, the rats were individually placed in the light room for 60s, the guillotine door was raised. As the rat entered the dark compartment, the door was closed and a single electrical foot shock (0.5mA, 2s) was delivered through the grid floor using an isolated stimulator. Subsequently, the memory trial by the passive avoidance test was evaluated on the next day. Both the habituation and memory trail were without any electrical foot shock. The initial latency to enter the dark compartment was recorded before inducing the electrical shock. Moreover, in the memory trial, the step-through latency was measured with the dark room entrance delays up to a maximum duration of 300s. The total dark stay time was recorded as memory consolidation and/or storage of new information. As such, the number of entrances on day 1 was measured as the rat's mobility rate (Kalantarzadeh et al., 2020). The passive avoidance test determined the animal's ability to remember the received foot shock. Avoidance to enter the dark compartment and even longer stay in the light room were both interpreted as a positive response.

Statistical analysis

All data were expressed as mean±SEM and analyzed by analysis of variance (ANOVA) test, followed by LSD post-hoc testing for multiple groups. The comparisons between the initial latency and step-through latency (within-groups) were analyzed using the paired sample t-test. A *P*-value less than 0.05 was considered statistically significant. Notably, the calculations were performed using SPSS v.24.

Results

In this study, the Co and Sh groups exhibited no significant differences in their behavioral tests. Therefore, the Co group was selected as the reference of all following comparisons (Figures 1-4). In Figure 1, the initial and step-through latencies from the passive avoidance test are represented. No significant differences were seen in the values of initial latency in all experimental groups (Figure 1A). However, the step-through latency significantly ($P<0.01$) decreased in the Dep group compared to the Co group (Figure 1B). Moreover, the values of step-through latency were significantly higher in the Dep-Exe, Dep-Esc20 and Dep-Esc20-Exe groups ($P<0.05$ in Dep-Exe and Dep-Esc20; $P<0.01$ in Dep-Esc20-Exe) than the Dep group (Figure 1B). This indicated that escitalopram 20mg/kg accompanied by exercise had an additive effect on improving memory in rats with depression. However, no significant differences were seen in the values of step-through latency in the Dep-Rest, Dep-Esc10 and Dep-Esc10-Exe groups compared to the Dep group. This indicated that a rest duration after depression, usage of escitalopram at a dose of 10mg/kg with and without exercise did not have any considerable impact on alleviating the depression-induced memory deficits (Figure 1B).

To evaluate the within-group latency changes, the values of initial and step-through latency were analyzed using a paired sample t-test. Significant differences were detected between the initial and step-through latencies in all groups ($P<0.001$ in Co, Sh, Dep-Rest, Dep-Exe, Dep-Esc20 and Dep-Esc20-Exe groups; $P<0.01$ in Dep-Esc10 and Dep-Esc10-Exe groups; $P<0.05$ in Dep group; Figure 2). As observed in this figure, the occurrence of learning was indicated in all experimental groups, even though it occurred at different levels. Its lowest level was seen in the depression group.

Total dark compartment stay time

As illustrated in Figure 3, the dark stay time was significantly higher in the Dep, Dep-Rest, Dep-Esc10 and Dep-Esc10-Exe groups compared to the Co group ($P<0.01$ in Dep, Dep-Rest and Dep-Esc10; $P<0.05$ in Dep-Esc10-Exe). Therefore, being exposed to depression seems to have severely disrupted the memory consolidation in such a way that neither the rest period nor using escitalopram at a dose of 10mg/kg/day (with or without exercise) could have improved the storage of new information in rats with depression. In the Dep-Exe, Dep-Esc20 and Dep-Esc20-Exe groups, there were significant decreases ($P<0.01$, $P<0.05$ and $P<0.01$, respectively) in dark stay time compared to the Dep group. Moreover, in the Dep-Esc10 and Dep-Esc10-Exe groups, the dark stay had significant enhancements ($P<0.05$ in both) compared to the Dep-Exe group, that indicated the negative effects of a 10mg/kg dose of es-

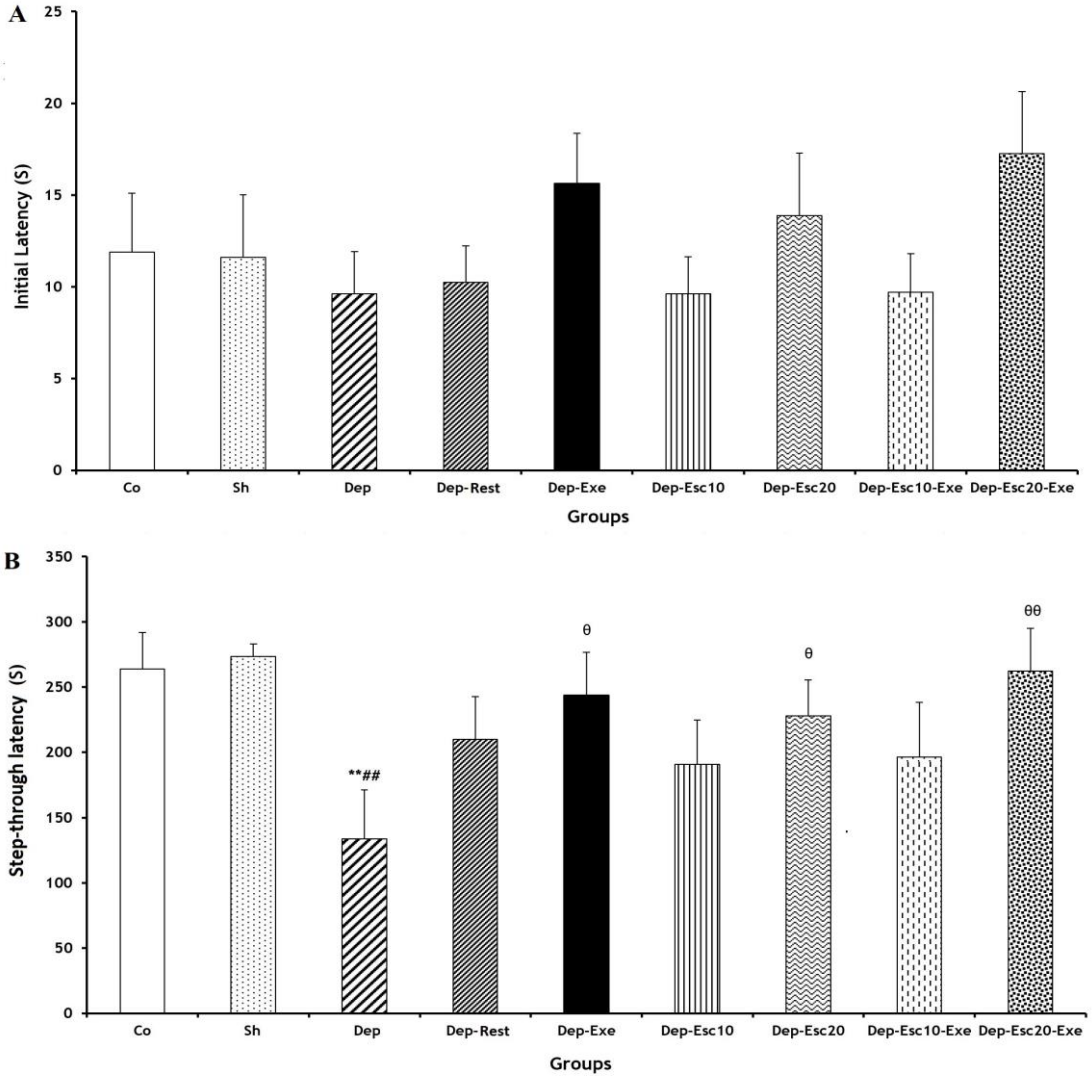

FIGURE 1. A) Initial latency and **B)** Step-through latency to entrance into the dark room of the passive avoidance apparatus for all groups before and after receiving a foot shock, respectively (n=8). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test). $^{**}P<0.01$ compared to Co group; $^{\#\#}P<0.01$ compared to Sh group; $^{\Theta}P<0.05$ and $^{\Theta\Theta}P<0.01$ compared to Dep group. Co: Control group, Sh: Sham group, Dep-Rest: Depression-Rest group, Dep: Depression-Depression group, Dep-Exe: Depression-Exercise group, De-Esc 10: Depression-Escitalopram 10mg/kg group, **De-Esc20:** Depression-Escitalopram 20mg/kg group, Dep-Esc10-Exe: Depression-Escitalopram10- Exercise, Dep-Esc20-Exe: Depression-Escitalopram20- Exercise.

citalopram on memory consolidation. Finally, the dark stay time was significantly ($P<0.05$) lower in the Dep-Esc20-Exe group in comparison with the Dep-Esc10-Exe group. Similar to the results concerning the Dep-Exe group, also using escitalopram at a dose of 20mg/kg could improve the memory consolidation in rats with depression compared to allowing a rest period after depression (Figure 3).

Number of entries to the dark room

According to Figure 4, the number of entrances into the dark compartment in the Dep-Exe and Dep-Esc20-Exe groups showed significant declinations ($P<0.05$ and $P<0.01$, respectively) compared to the Co group. Besides, the number of entries to the dark room significantly decreased ($pP<0.05$) in both Dep-Exe and Dep-Esc20-Exe groups compared to the Dep-Rest group.

Discussion

The present study compared the therapeutic effects of exercise, using escitalopram at different doses (10 and 20 mg/kg) and exercise-accompanied escitalopram on different aspects of brain functions, such as learning, memory, memory consolidation and locomotor activity in rats with depression induced by chronic stress.

The research findings represented that depression not

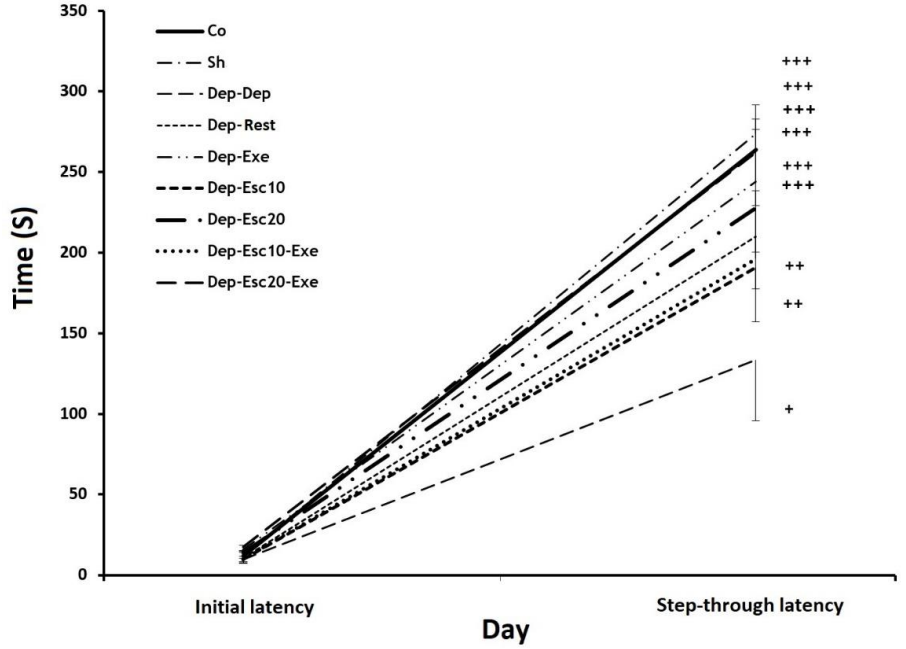

FIGURE 2. Initial latency and step-through latency to entrance into the dark room of the passive avoidance apparatus before and after the foot shock (within-group) (n=8). Results are expressed as mean±SEM (Paired sample t-test). $^{+}P<0.05$, $^{++}P<0.01$ and $^{+++}P<0.001$ initial latency relative to the step-through latency. Co: Control group, Sh: Sham group, Dep-Rest: Depression-Rest group, Dep: Depression-Depression group, Dep-Exe: Depression-Exercise group, De-Esc10: Depression-Escitalopram 10mg/kg group, De-Esc20: Depression-Escitalopram 20mg/kg group, Dep-Esc10-Exe: Depression-Escitalopram10- Exercise, Dep-Esc20-Exe: Depression-Escitalopram20- Exercise.

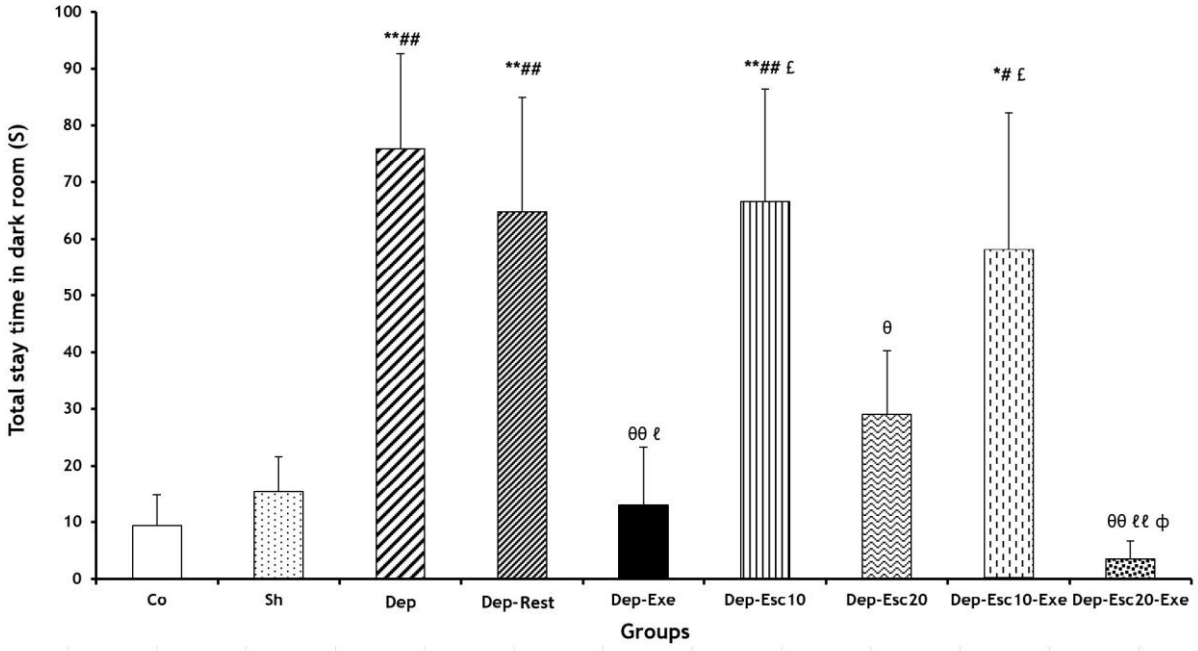

FIGURE 3. Total stay time in dark room of the passive avoidance apparatus for all groups 1 day after receiving the foot shock (n=8). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test). *P<0.05 and **P<0.01 compared to Co group; #P<0.05 and ##P<0.01 compared to Sh group; ΘP<0.05 and ΘΘP<0.01 compared to Dep group; ℓP<0.05 and ℓℓP<0.01 compared to Dep-Rest group, £P<0.05 compared to Dep-Exe group, ϕP<0.05 compared to Dep-Esc10-Exe group. Co: Control group, Sh: Sham group, Dep-Rest: Depression-Rest group, Dep: Depression-Depression group, Dep-Exe: Depression-Exercise group, De-Esc 10: Depression-Escitalopram 10mg/kg group, De-Esc 20: Depression-Escitalopram 20mg/kg group, Dep-Esc10-Exe: Depression-Escitalopram10- Exercise, Dep-Esc20-Exe: Depression-Escitalopram20- Exercise.

only decreased the level of learning but also severely impaired memory and memory consolidation. These findings are similar to the results of previous studies on the models of depression that were induced by chron-

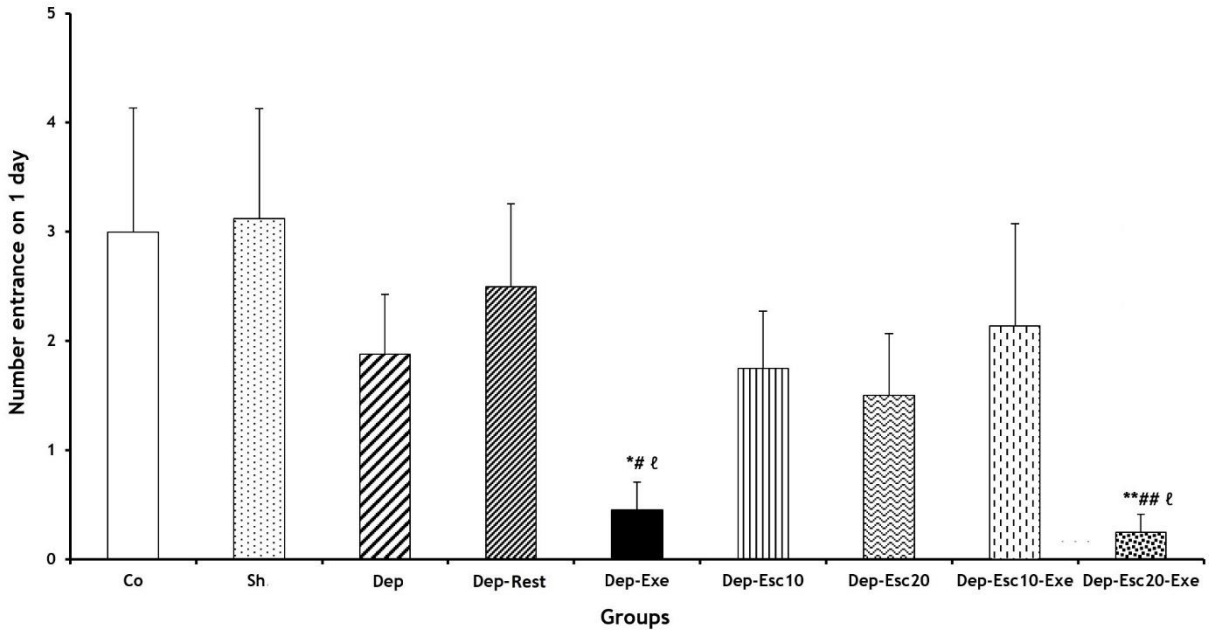

FIGURE 4. The number of entrances to the dark room in the passive avoidance apparatus for all groups 1 day after receiving the foot shock (n=8). Results are expressed as mean±SEM (ANOVA test, LSD post-hoc test). $^{*}P<0.05$ and $^{**}P<0.01$ compared to Co group; $^{\#}P<0.05$ and $^{\#\#}P<0.01$ compared to Sh group; $^{\ell}P<0.05$ compared to Dep-Rest group. Co: Control group, Sh: Sham group, Dep-Rest: Depression-Rest group, Dep: Depression-Depression group, Dep-Exe: Depression-Exercise group, De-Esc 10: Depression-Escitalopram 10mg/kg group, De-Esc 20: Depression-Escitalopram 20mg/kg group, Dep-Esc10-Exe: Depression-Escitalopram10- Exercise, Dep-Esc20-Exe: Depression-Escitalopram20- Exercise.

ic stress and their role in affecting various brain functions, such as memory, brain activities, gene expressions and the biochemical biomarkers changes, including the brain-derived neurotrophic factor (BDNF) levels (Napolitano et al., 1999; Roceri et al., 2002). Furthermore, it has been reported that not only chronic stress, but also depression probably affected memory consolidation via altering some hormones like glucocorticoids that will consequently change BDNF levels (Finsterwald and Alberini, 2014; Roozendaal, 2002). Both the basolateral amygdala, which is an important memory modulatory structure, and the interactions between different brain regions may potentially impact memory consolidation in subjects under chronic stress and probably those with depression too (Roozendaal, 2002).

The majority of performed treatment methods in this study displayed positive effects on alleviating the depression-induced memory deficits. Also, exercise, escitalopram at a dose of 20mg/kg and escitalopram 20mg/kg accompanied by exercise not only counteracted the memory deficits, but also increased memory consolidation under depression conditions. Nevertheless, previous studies had discussed different views on the efficacy of escitalopram and exercise. For instance, the positive effects of both exercise and escitalopram on memory consolidation have been discussed in some studies (Bhagya et al., 2011; Neves et al., 2015). It has been shown that escitalopram had improved different types of memory in subjects with depression (Soczynska et al., 2014). Moreover, it was demonstrated that exercise elevated cognitive functions and overall brain health (Motaghinejad et al., 2015) through various mechanisms that affect brain functions; for instance, the augmentation of antioxidant defense mechanisms, as well as activation of brain plasticity, neurogenesis and brain metabolic capacity could be mentioned (Cui et al., 2009; Ding et al., 2006; Liu and Nusslock 2018). However, some studies have shown that physical activities and particularly forced exercise act as stressors and impair memory (Arida et al., 2004; Leasure and Jones, 2008). It seems that exercise may potentially influence some brain mediators, such as serotonin, noradrenaline, dopamine and corticosterone levels (Lin and Kuo, 2013; Radahmadi et al., 2015). Chennaoui et al. (2000) proposed that exercise could increase hippocampal serotonin levels. Contrastingly, in other studies, it is reported that exercise did not change the concentration of serotonin in some brain regions (Chen et al., 2008). Therefore, the impact of exercise on serotonin receptors has been region-specific in the brain (Greenwood et al., 2005; Maniam and Morris,

2010).

An important finding in this research was that a higher dose of escitalopram (20mg/kg) with and without exercise (particularly with exercise) alleviated memory deficits in subjects with depression, whereas its lower dose (10mg/kg) had no effect on the improvement of brain functions. Based on current findings, the effects of using escitalopram at a dose of 10mg/kg on brain functions were similar to having a rest period after depression. As the dosage of escitalopram was increased, the possibility of gaining beneficial effects was also enhanced (Zhong et al., 2012). Hence, a high dose of escitalopram had a positive effect on the depression treatment processes (Couto et al., 2012). However, previous studies reported positive and negative effects, and even no impact on the improvement of memory for the usage of escitalopram at a dose of 10mg/kg (Bhagya et al., 2011; Jacobsen and Mørk 2004; Yilmaz et al., 2011). Accordingly, a study reported similar results on the ineffectiveness of escitalopram at a dose of 10mg/kg on some important memory-related parameters, such as N-methyl-D-aspartate receptors (Yilmaz et al., 2011), hippocampal BDNF levels and serotonin receptor expression (Henn et al., 2020). In some studies, escitalopram at a dose of 10mg/kg was shown to have decreased BDNF protein in the frontal cortex and the hippocampus of the rat's brain (Jacobsen and Mørk, 2004). However, the positive effects of chronically using a 10mg/kg dose of escitalopram have been observed on various memory aspects too (Bhagya et al., 2011).

Additionally, based on recent findings, exercise alone exhibited better performance on memory improvement and consolidation compared to only using a dose of 10mg/kg/day escitalopram in subjects with depression. Escitalopram at a dose of 10mg/kg/day represented non-significant inhibitory effects in the escitalopram10-exercise group on the treatment of depression-induced memory impairments compared to the exercise without the use of escitalopram in subjects with depression. Nevertheless, using escitalopram at a dose of 10mg/kg showed no significant enhancement on memory improvement in subjects with depression. This may be related to the delay time, (approximately two weeks) needed for the therapeutic responses of SSRIs drugs to be efficacious. Inevitably, this delayed onset seems to be because of the neuro-adaptive changes in the brain (Piñeyro and Blier, 1999). In this regard, a sustained administration of escitalopram elevates extracellular serotonin levels. This leads to the activation of serotonin autoreceptors on serotonergic neurons. Subsequently, this activation results in suppressing the spontaneous firing of serotonergic neurons that in rats could return to the control rate, approximately, after two weeks (El Mansari et al., 2005). Therefore, in response to the prolonged serotonin elevation in the chronic antidepressant treatment, the serotonin autoreceptor appeared to be desensitized (El Mansari et al., 2005; Piñeyro and Blier, 1999). However, exercise (from the beginning) enhances the serotonergic system by activating the serotonergic neuronal firing (excitability) (Dremencov et al., 2015). It also decreases the serotonin transporters that would transport serotonin from the synaptic cleft back to the presynaptic neuron (Greenwood et al., 2005) and diminishes the expression of serotonin autoreceptors (Maniam and Morris, 2010).

As mentioned above, a dose of 20mg/kg of escitalopram with and without exercise showed therapeutic effects on ameliorating memory in subjects with depression. Although, the combination of escitalopram 20mg/kg with exercise showed no significant additive effect on depression-induced memory impairments compared to the exercise alone. The common mechanisms underlying both of these protocols can be the cause of brain function improvements. For instance, the changes in levels of growth factors, BDNF and corticosterone are some of these mechanisms (Benatti et al., 2018; Liu and Nusslock, 2018; Radahmadi et al., 2015; Schulte-Herbrüggen et al., 2009).

According to available data, locomotor activity was decreased by exercise and exercise-accompanied escitalopram at a dose of 20mg/kg in the subjects with depression. Previous studies had demonstrated the positive, negative and neutral effects of escitalopram on locomotor activity (Kamińska et al., 2018; Li et al., 2015; Sağlam et al., 2006). These contrasting views might be due to the changes in dopamine levels (Schindler and Carmona, 2002) and/or inhibition of dopamine neuron firing in some brain areas (Dremencov et al., 2009). However, the types and duration of drug administration, depression, as well as behavioral tests are also effective factors for the role escitalopram plays in memory processing and locomotor activity. Finally, although different factors (e.g., the type behavioral test) could affect locomotor activity, it is reported that the exercise-induced fatigue reduced levels of dopamine neurotransmission

in some brain regions (Foley and Fleshner, 2008).

Conclusion

To sum up, depression had negative effects on brain functions, such as memory and memory consolidation. The therapeutic effects of exercise, escitalopram at a dose of 20mg/kg and escitalopram at the same dose (20mg/kg) accompanied by exercise (escitalopram20 mg/kg with and without exercise) on memory improvement were observed in subjects with depression. Additionally, a 10mg/kg dose of escitalopram had non-significant inhibitory effects on the treatment of depression-induced memory impairments in exercise-accompanied escitalopram at a dose of 10mg/kg compared to the exercise alone in subjects with depression. Finally, exercise, a higher dose of escitalopram (20mg/kg) with and without exercise (especially with exercise) all alleviated memory deficits in subjects with depression. Also, there was a partial additive effect of escitalopram at a dose of 20mg/kg accompanied with exercise (in reversing the memory deficit). Conclusively, the exercise-accompanied escitalopram (20mg/kg) seems to be the best depression treatment protocol for the subjects with depression. However, still further investigations, such as molecular, electrophysiological and biochemical research studies are required to trace and clarify the mechanism(s) involved.

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Conflict of interest

The authors declare no conflict of interests.

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