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Original Article

The protective effects of escitalopram on chronic restraint stress-induced memory deficits in adult rats

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ABSTRACT

Introduction: Stress influences brain functions adversely but escitalopram exhibits positive effects on cognitive processes. Therefore, this study investigated the protective effects of different escitalopram doses on cognitive functions in rats under chronic stress and normal conditions.

Methods: Forty-nine rats were randomly allocated into seven groups: control, sham, stress, escitalopram (10, 20 mg/kg/day) and stress-escitalopram (both doses). Initial latency, latency after 1-day, dark stay (DS) time and the number of entrances to the dark compartment were evaluated by passive avoidance test.

Results: There were significant latency differences in stress and escitalopram10 groups compared to control group. Additionally, latencies showed significant enhancements in both 10 and 20 mg/kg/day stress-escitalopram groups compared to stress group and significant decrease in escitalopram20 group with respect to escitalopram10 group. DS time was significantly higher in stressed group and significantly lower in escitalopram10 groups, both compared to control group. Also, it was significantly lower in both stress-escitalopram groups in comparison with stress group. Furthermore, escitalopram20 group had a significantly higher DS time compared to escitalopram10 group. Finally, the number of entrances to the dark compartment was significantly lower in stress, escitalopram10 and stress-escitalopram10 groups compared to control group.

Conclusion: Different doses of escitalopram affected brain functions under chronic stress and normal conditions. Escitalopram10 presented the most beneficial effects on improving brain functions under normal conditions. Whereas, both escitalopram doses showed similar protective effects on memory under stress. Overall, escitalopram at a dose of 10 mg/kg/day improved learning, memory consolidation and locomotor activity better than its maximum dose of 20 mg/kg/day.

Keywords:
Escitalopram
Stress
Learning
Memory
Passive avoidance

Introduction

Stress is an internal response to harmful stimuli (internal and external) that affect cognitive functions (Rafdahmadi et al., 2017; Simoens et al., 2007). As such, it is reported that all kinds of stress, especially psychological stress, disrupt brain functions to a great extent (Patki et al., 2013; Tran et al., 2010). Even though stress is an inseparable mechanism of human life, it is rather chronic stress that activates the hypothalamic-pituitary-adrenal (HPA) axis and leads to the secretion of glucocorti-

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coids that will eventually disturb many brain activities, such as learning and memory consolidation (Ghadrdoost et al., 2011; Hadad-Ophir et al., 2014). Conversely, escitalopram is a highly efficient antidepressant belonging to a class of selective serotonin reuptake inhibitors (SSRIs) that is widely used in depression treatments (Montgomery et al., 2001). Also, since it is an active S-enantiomer of citalopram (Montgomery et al., 2001), it is associated with anti-anxiety, -fear and -depressant activities; so, it is sometimes used in the treatment of both stress and anxiety (Kirino, 2016; Lim et al., 2010). Moreover, escitalopram has been often suggested for its anti-anxiety and anti-stress characteristics probably due to its mild and tolerable side-effects (Montgomery et al., 2001). The dual-action antidepressants acting on both serotonin and noradrenaline pathways, that it has been considered responsible for the superior efficacy of escitalopram over other conventional SSRIs in anxiety disorder treatment (Murdoch and Keam, 2005). Some studies have suggested that SSRIs, including escitalopram, may be effective in reversing the learning disabilities and improving memory due to being involved in various mechanisms, such as increasing the serotonin levels in the hippocampus and prefrontal cortex (Azorin et al., 2004; Bhagya et al., 2011; Waugh and Goa, 2003), regulating the HPA axis activity (Azorin et al., 2004; Waugh and Goa, 2003), altering the synaptic flexability in neural circuits (Li et al., 2015) and increasing the brain mediators (Bhagya et al., 2011; Ibrahim et al., 2019; Wu et al., 2018). Nevertheless, other studies have highlighted the negative effects of escitalopram on cognitive performance (Jensen et al., 2014). Despite all previous literature on escitalopram, there is still no published report on the protective impact of using escitalopram at different doses on various aspects of cognitive functions under chronic stress and normal states. Nowadays, people are exposed to different types of psychological and emotional stress. Therefore, restraint stress was selected as a strong emotional stress model in this study (Patchev and Patchev, 2006; Ranjbar et al., 2016; Wood et al., 2003). The impact of using this drug on brain functions under certain stressful conditions, such as the predictable stressful and/or conflict/war situations in which individuals may be aware of the condition from the beginning, is not clear yet.

All in all, the present study was designed and conducted to investigate the protective effects of different escitalopram doses on learning, memory, locomotor activity and memory consolidation under chronic stress and normal conditions.

Material and methods

Animals

Forty-nine adult male Wistar rats (200–250g) were procured from the Isfahan University of Medical Sciences in Iran. The rats were maintained under 12h light/dark cycles (lights on from 7:00 to 19:00) under controlled temperature (22±2°C) and humidity (50±5%). Food and water were made available *ad libitum*, except during the stress sessions. All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23, 2011 Revision); also, the procedures and protocols were approved by the Animal Use Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.555). A period of two weeks was allowed for adaptation before animals were randomly assigned to the following seven groups (n=7 per group): control (CO) group, in which the rats were maintained in the cage with no special treatment; sham (Sh) group, in which the rats only received saline injections; stress (St) group, in which the rats were exposed to restraint stress (6h/day); escitalopram10 (Esc10) group, in which the rats were injected 10 mg/kg/day of escitalopram; escitalopram20 (Esc20) group, in which the rats were injected 20 mg/kg/day of escitalopram; stress-escitalopram10 (St-Esc10) group, in which the rats were exposed to stress and received 10mg/kg of escitalopram prior to being exposed to stress and stress-escitalopram20 (St-Esc20) group, in which the rats were exposed to stress and received 20mg/kg of escitalopram prior to the stress. The experiment duration was 14 consecutive days for all groups.

Drugs

Escitalopram was purchased (Sobhan Daru Co., Iran) in powder form, then dissolved in sterile physiological saline for intraperitoneal injections at the doses of 10 and 20 mg/kg/day for 14 consecutive days in the stressed groups exactly before being exposed to stress. In previous studies on rats, different doses of escitalopram (1–20 mg/kg) were used (Jastrzębska et al., 2017; Kaminska and Rogoz, 2016). Most of these studies used a dose of 5mg/kg and below to investigate the fear

treatment methods (Benatti et al., 2014; Sánchez et al., 2003). However, higher doses (10 and 20mg/kg, as the optimum and maximum ones respectively), were used for the treatment of stress, anxiety and depression (Seo et al., 2019; Yang et al., 2015). The half-life of escitalopram could be shortened to 15–20% of humans (≈27–33h) due to the rapid metabolism in rats (Bourke et al., 2013; Bundgaard et al., 2007; Murdoch and Keam, 2005). Also, escitalopram has displayed an approximate 7-day period of effective treatment in several behavioral depression models (Montgomery et al., 2001)(Sattin, 2008 #41). At last, rats in sham group received only equal volumes of saline.

Stress procedure

Restraint stress is defined as a kind of strong psychological stress in rodents (Patchev and Patchev, 2006; Ranjbar et al., 2016; Wood et al., 2003). To induce this stress model, rats were placed in cylindrical restrainers for 6 h/day (from 8:00 to 14:00) for 14 consecutive days.

Passive avoidance apparatus

The shuttle box (20×25×64cm) was used as the passive avoidance apparatus for measuring different aspects of cognitive functions, such as learning, memory, consolidation and locomotor activity (Kalantarzadeh et al., 2020). This apparatus had two identical light and dark compartments with sliding guillotine doors and a grid floor. The test was conducted in three phases (overall 300s), namely, habituation (with no electrical foot shock on day 12), learning trial (with electrical foot shocks on day 13) and memory trial (with no electrical foot shock on day 14). A single electric shock (0.5mA, 50v and 2s) was delivered to the animal's foot through the grid floor during the learning trial. The initial latency (IL) time to enter the dark compartment was recorded before inducing the electricalshock. Also, the latency time of entry to the dark compartment was measured after 1 day (up to a maximum delay of 300s). The difference between the IL and latency after 1 day was interpreted as the occurrence of learning in the experiment (Kalantarzadeh et al., 2020; Radahmadi et al., 2015). Also, the total dark stay (DS) time was considered as either the memory consolidation or storage of new information. In addition, the number of entrances to the dark compartment was recorded as the locomotor activity (Kalantarzadeh et al., 2020; Shabani et al., 2012; Vohora et al., 2000).

Statistical analysis

All behavioral data were analyzed by one-way ANOVA followed by LSD post-hoc test for multiple groups (between-groups). Initial latency and latency after 1 day (within-group) were compared and analyzed using the paired sample t-test. All data were reported as mean±-SEM. The value of $P<0.05$ was considered statistically significant. Notably, the calculations were performed using IBM SPSS Statistics v.24.

Results

Figures 1A and 1B respectively show IL and latency after 1 day for all experimental groups. Since the Co and Sh groups exhibited no significant differences in their behavioral tests, the Co group was selected as the reference for all following comparisons. Concerning the IL values, no significant differences were observed in any group (Figure 1A). Also, the values of latency after 1 day in the St and Esc10 groups were significantly ($P<$-0.05 in both) lower and higher, respectively, than in the Co group. These data indicate that memory is declined due to stress and enhanced as a result of using escitalopram at a dose of 10 mg/kg/day in normal subjects (Figure 1B). Moreover, the latency after 1 day decreased significantly ($P<0.05$) in the Esc20 group in comparison with the Esc10 group, representing the effect of drug doses on memory in normal subjects (Figure 1B).

In both St-Esc10 and St-Esc20 groups, the latency after 1 day showed significant ($P<0.05$) enhancements in comparison with the St group; this shows the role of both escitalopram doses in improving memory. Finally, the latency did not have any significant difference in the St-Esc20 group compared to the Esc20 group (Figure 1A). As illustrated in Figure 2, IL and latency after 1 day were analyzed to evaluate within-group latency changes. Significant differences were detected between IL and latency after 1 day in all experimental groups. This indicated that different levels of learning occurred in all groups. For instance, the level of learning happened at the lowest and highest levels in the St group and the highest level in the Esc10 group, respectively (Figure 2).

In the St and Esc10 groups, the total DS times had significant ($P<0.05$, in both) differences compared to the Co group, which indicates a decrease and enhancement of memory consolidation, respectively, by stress

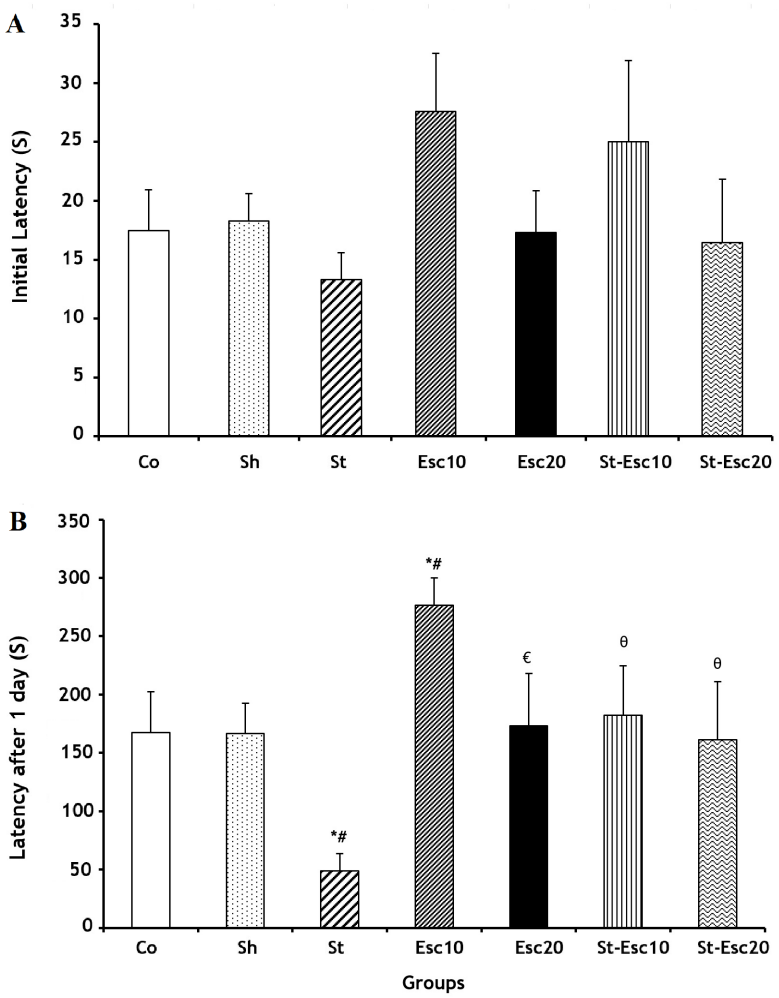

FIGURE 1. A: Initial latency and B: latency after 1 day to entrance into the dark room of the passive avoidance apparatus for all groups before and after receiving a foot shock, respectively (n=7 in each group). Results are expressed as mean±SEM (ANOVA test, LSD post- hoc test). $^{*}P<0.05$ compared to the Co group; $^{\#}P<0.05$ compared to the Sh group; $^{\theta}P<0.05$ compared to the St group; $^{€}P<0.05$ compared to the Esc10 group. Co: Control group; Sh: Sham group; St: Stress group; Esc10: Escitalopram 10 mg/kg/day; Esc20: Escitalopram 20 mg/kg/day; St-Esc10: Stress-Escitalopram 10 mg/kg/day; St-Esc20: Stress-Escitalopram 20 mg/kg/day.

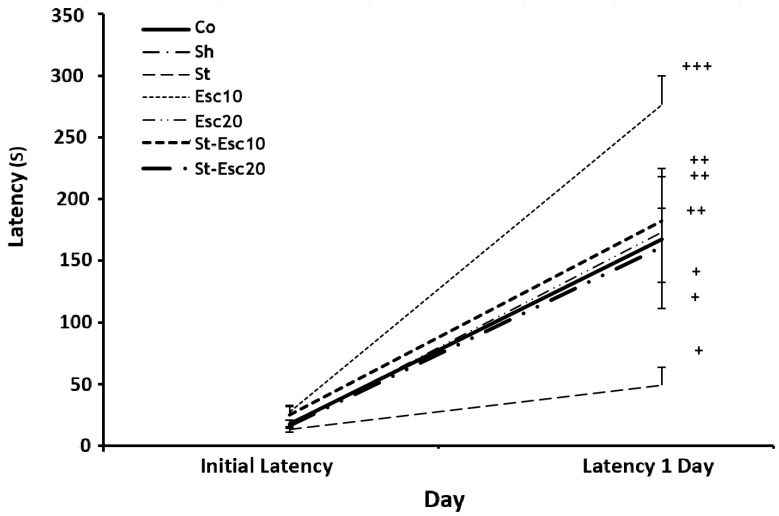

FIGURE 2. Initial latency and latency after 1 day to entrance into the dark room of the passive avoidance apparatus before and after the foot shock (within-group) (n=7 in each group). Results are expressed as mean±SEM (Paired sample t-test). $^{+}P<0.05$, $^{++}P<0.01$ and $^{+++}P<0.001$ initial latency relative to the latency after 1 day. Co: Control group; Sh: Sham group; St: Stress group; Esc10: Escitalopram 10 mg/kg/day; Esc20: Escitalopram 20 mg/kg/day; St-Esc10: Stress-Escitalopram 10 mg/kg/day; St-Esc20: Stress-Escitalopram 20 mg/kg/day.

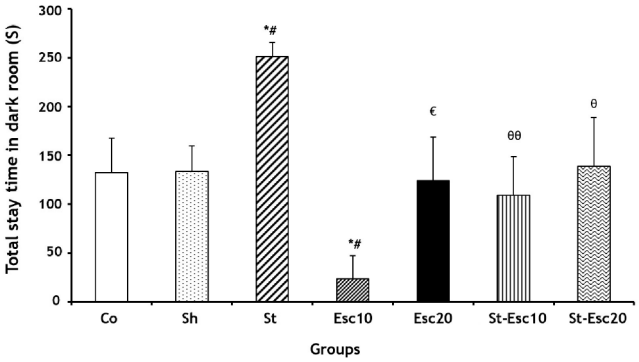

FIGURE 3. Total stay time in dark room of the passive avoidance apparatus for all groups 1 day after receiving the foot shock (n=7 in each group). Results are expressed as mean±SEM (ANOVA test, LSD post- hoc test. $^{*}P<0.05$ compared to the Co group; $^{\#}P<0.05$ compared to the Sh group; $^{\theta}P<0.05$ and $^{\theta\theta}P<0.01$ compared to the St group; $^{€}P<0.05$ compared to the Esc10 group. Co: Control group; Sh: Sham group; St: Stress group; Esc10: Escitalopram 10 mg/kg/day; Esc20: Escitalopram 20 mg/kg/day; St-Esc10: Stress-Escitalopram 10 mg/kg/day; St-Esc20: Stress-Escitalopram 20 mg/kg/day.

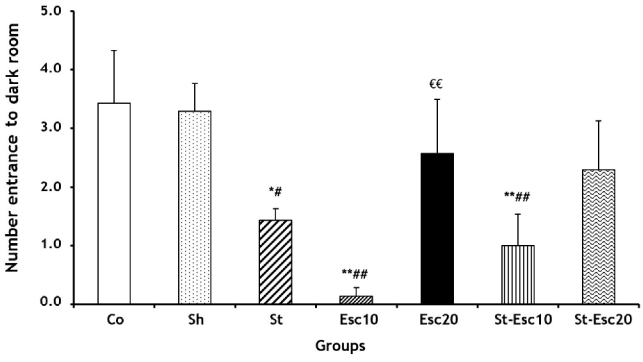

FIGURE 4. The number of entrances to the dark room in the passive avoidance apparatus for all groups 1 day after receiving the foot shock (n=7 in each group). Results are expressed as mean±SEM (ANOVA test, LSD post- hoc test. $^{*}P<0.05$ and $^{**}P<0.01$ compared to the Co group; $^{\#}P<0.05$ and $^{\#\#}P<0.01$ compared to the Sh group; $^{€€}P<0.01$ compared to the Esc10 group. Co: Control group; Sh: Sham group; St: Stress group; Esc10: Escitalopram 10 mg/kg/day; Esc20: Escitalopram 20 mg/kg/day; St-Esc10: Stress-Escitalopram 10 mg/kg/day; St-Esc20: Stress-Escitalopram 20 mg/kg/day.

and escitalopram 10 (Figure 3). There were significant ($P<0.05$ in both) enhancements in the total DS time of the St-Esc20 and St-Esc10 groups compared to the St group. Finally, the total DS time was significantly ($P<0.05$ in both) lower than the St group in both St-Esc10 and St-Esc20 groups, which indicates that the improving effects of memory consolidation were ameliorated by both doses of escitalopram. However, significantly ($P<0.05$) lower memory consolidation was seen in the Esc20 group compared to the Esc10 group under normal conditions; therefore, the destructive effects of escitalopram on memory consolidation were seen with higher doses. Finally, concerning the DS time, no significant differences were seen between St-Esc10 and Esc10 groups, or between the St-Esc20 group and the Esc20 group (Figure 3).

The number of entrances to the dark compartment showed significant differences in the St, ($P<0.05$), Esc10 ($P<0.01$) and St-Esc10 ($P<0.01$) groups compared to the Co group (Figure 4). As shown in Figure 4, the number of entrances to the dark compartment was significantly ($P<0.01$) higher in the Esc20 group compared to the Esc10 group; this is indicating an increased locomotor activity at a dose of 20 mg/kg/day of escitalopram compared to 10 mg/kg/day under normal conditions. At last, there was no significant difference in the number of entrances to the dark compartment between the St-Esc10 and St-Esc20 groups (Figure 4).

Discussion

In the current study, the protective effects of different doses of escitalopram (10 and 20 mg/kg/day) were investigated on cognitive functions, such as learning, memory, memory consolidation and locomotor activity in rats under chronic stress and normal condition.

The findings of this research represent an occurrence of learning in all experimental groups at different levels, including the stressed group even though at a lower level. Nevertheless, some studies have confirmed that stress accelerates the onset and severity of cognitive impairments, such as learning and memory (Bahramzadeh Zoeram et al., 2019; Thai et al., 2013). Accordingly, learning impairment has also been indicated as a key component of post-traumatic stress disorder (Bui et al., 2013). On the other hand, it is reported that SSRI drugs, including escitalopram, may facilitate learning and reverse learning disabilities due to the increasing the serotonin levels in the brain (Bhagya et al., 2011; Ceglia et al., 2004). Also, it is reported that escitalopram reversed memory deficits induced by maternal separation in the rat (do Couto et al., 2012). Therefore, different doses of escitalopram may seemingly get involved in a paradoxical reversal learning paradigm (Drozd et al., 2019).

In the present study, stress destructed memory and memory consolidation sharply. Also, some studies have proven that exposure to different types of stressors leads to the impairment of cognitive processes, such as mem-

ory (do Nascimento et al., 2019; Ulrich-Lai and Herman, 2009) and memory consolidation (Sardari et al., 2015). As such, different mechanisms were proposed for the stress-induced changes in cognitive performance, including the alteration of various biochemical substances, hormones, neurotransmitters, brain-derived neurotrophic factor (BDNF), oxidative stress, as well as the morphological changes like dendritic spine density in specific brain areas (Diamond et al., 2006; McGaugh and Roozendaal, 2002; Patki et al., 2013; Zoladz et al., 2012).

According to present findings, escitalopram at a dose of 10 mg/kg/day (but not 20 mg/kg/day) increased memory and memory consolidation in normal subjects. However, a desirable cognitive enhancement by SSRIs is reported as well (Mowla et al., 2007; Ren et al., 2015). Moreover, it is shown that escitalopram (10 mg/kg) neither prevents the recognition memory impairment in the rats with 5-HT depletion (Riga et al., 2020), nor does it inhibit the dizocilpine-induced spatial memory deficit (Tao et al., 2016). Rose et al. (2006) indicated that escitalopram did not affect cognitive functions in healthy individuals. However, the drug dose seems to affect memory under normal conditions. As such, different doses of escitalopram may lead to the participation of various signaling pathways in brain functions (Ren et al., 2015; Wang et al., 2016).

Another finding of this study confirmed that both optimum and maximum doses of escitalopram (respectively, 10 and 20 mg/kg/day for rodents) improved the stressed-induced memory deficit in a similar way. Therefore, different doses of escitalopram had similar protective effects for improving memory and memory consolidation under stress conditions in contrast to the normal ones. In addition, escitalopram neutralized the destructive stress-related effects on memory. In comparison with the normal conditions, stress slowed down the improvement rate of brain functions. Similarly, previous studies had demonstrated that escitalopram might improve stress-induced memory deficits (do Couto et al., 2012; Ma et al., 2015; Xi et al., 2011). Also, escitalopram may probably affect memory by increasing serotonin and/or dopamine in the brain (Montezinho et al., 2010; Schilström et al., 2011). As such, escitalopram can not only alter synaptic plasticity in the neural circuits (Li et al., 2015), but also improve hippocampal-dependent memory under chronic stress (do Couto et al., 2012). By contrast, some studies focused on the negative impact of escitalopram on cognitive performance (Jensen et al., 2014). The drug type, timing and duration of treatment as well as the stress type may influence the cognitive performance. However, chronic escitalopram treatment somewhat reversed the cognitive dysfunction probably by activating some signaling pathways (Ibrahim et al., 2019), regulating the HPA axis activity (Wu et al., 2018), altering BDNF levels (Aboukhatwa et al., 2010), synaptic levels of serotonin (Msetfi et al., 2016) and vascular endothelial growth factor mediated angiogenesis (Ma et al., 2015).

Based on other findings here, stress decreased locomotor activity. Therefore, stress duration may perturb physiological functions, consequently leading to other associative depression disorders (Chang and Grace, 2014; Yang et al., 2015) and reduction of stress-related locomotor activity (Pechlivanova et al., 2011). There are paradoxical reports on the effects of stress on locomotor activity; for instance, reduction of locomotor activity (Gammoh et al., 2017; Mortazaei et al., 2019), enhancement of locomotor activity (Yang et al., 2015) and no stress-related effects (Duque et al., 2016) are all discussed in various studies. Thus, duration and types of stress, as well as the behavioral assessment methods seem to have affected the locomotor activity results (Schöner et al., 2017).

Conversely, only escitalopram at a dose of 10mg/kg decreased locomotor activity in normal and stressed subjects. Therefore, the optimum dose of escitalopram may have caused more immobility under normal condition and stress conditions. Nevertheless, reduction of locomotor activity due to the application of escitalopram has been reported in both stressful and non-stressful situations (Gammoh et al., 2017). Lin et al. (2016) explained that escitalopram administration (10 mg/kg/day) even under stress conditions did not affect the rodent's motor activity. Yet, it has also been shown that escitalopram (10 mg/kg/day) increased locomotor activity under both stress and non-stress conditions (Yang et al., 2015). On the other hand, in our present study, escitalopram (20 mg/kg/day) did not result in locomotor activity treatment either with or without stress. Such a result highlights the impact of using different doses of escitalopram on locomotor activity. In a previous study, escitalopram at a dose of 20 mg/kg under normal conditions had shown no significant changes in locomotor ac-

tivity (Shetty et al., 2015). However, another study had demonstrated the role of escitalopram pre-treatment (10, 20 mg/kg) in improving the reduced motor function due to the enhancement of 3-nitropropionic acid in rodents (Shetty et al., 2015). All in all, escitalopram (20mg/kg) increased locomotor activity more than escitalopram (10mg/kg) in normal condition. Therefore, different drug doses seem to usually affect locomotor activity in normal conditions but not under stress conditions. These paradoxical results may indicate the influence of treatment duration, drug consumption manner, drug dose and the type of behavioral tests (Kalantarzadeh et al., 2020; Kaminska and Rogoz, 2016).

Notably, the limited number of rats in this study was based on ethical clearance for animal research. However, if this study can be validated by a larger sample group size, conclusions would be strengthened.

Conclusion

To sum up, different doses of escitalopram had various effects on brain functions under chronic stress and normal conditions. Escitalopram (10 mg/kg/day) displayed the most positive effects on the improvement of brain functions in normal situations. However, both doses of escitalopram showed similar protective effects on memory under stress conditions. Nonetheless, escitalopram at a dose of 10 mg/kg/day improved learning, memory consolidation and locomotor activity better than its dose of 20 mg/kg/day. However, further studies on the cellular, structural and biochemical aspects are required to clarify the underlying mechanisms that exerted the protective effects for escitalopram.

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Conflict of interest

The authors declare that they have no conflict of interest.

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