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Sildenafil prevents chronic psychosocial stress-induced working memory impairment: Role of brain-derived neurotrophic factor

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ABSTRACT

Background: Psychosocial stress, a common feature in modern societies, impairs cognitive functions. It is suggested that stress hormones and elevated excitatory amino acids during stress are responsible for stress-induced cognitive deficits. Reduced brain-derived neurotrophic factor (BDNF) levels, increased oxidative stress, and alteration of synaptic plasticity biomarkers are also possible contributors to the negative impact of stress on learning and memory. Sildenafil citrate is a selective phosphodiesterase type 5 (PDE5) inhibitor and the first oral therapy for the treatment of erectile dysfunction. It has been shown that sildenafil improves learning and memory and possesses antioxidant properties. We hypothesized that administering sildenafil to stressed rats prevents the cognitive deficit induced by chronic psychosocial stress.

Methods: Psychosocial stress was generated using the intruder model. Sildenafil 3 mg/kg/day was administered intraperitoneally to animals. Behavioral studies were conducted to test spatial learning and memory using the radial arm water maze. Then, the hippocampal BDNF level and several antioxidant markers were assessed.

Results: This study revealed that chronic psychosocial stress impaired short-term but not long-term memory. The administration of sildenafil prevented this short-term memory impairment. Chronic psychosocial stress markedly reduced the level of hippocampal BDNF ($P<0.05$), and this reduction in BDNF was normalized by sildenafil treatment. In addition, neither chronic psychosocial stress nor sildenafil significantly altered the activity of measured oxidative parameters ($P > 0.05$).

Conclusion: Chronic psychosocial stress induces short-term memory impairment. The administration of sildenafil citrate prevented this impairment, possibly by normalizing the level of BDNF.

1. Introduction

Learning and memory are distinct cognitive processes for acquiring and retaining information (Bailey et al., 1996; Lynch, 2004). The standard structure and function of the brain are altered by severe and/or long-term stress (McEwen, 2007). Chronic stress has been previously reported to impair learning and memory in animal models (Massadeh et al., 2021; Rababa'h et al., 2019a; Alzoubi et al., 2018; Alzoubi et al., 2009; Gerges et al., 2004) and humans (Lupien et al., 1997). The mechanism by which stress impairs memory is thought to be by elevating excitatory amino acid and glucocorticoid levels, which, in turn, induce excitotoxicity and hippocampal atrophy (McEwen, 1999).

BDNF is essential for the modulation of synaptic plasticity and the maintenance of neuronal viability (Bekinschtein et al., 2014). The neurotrophic impact of this substance has been linked to its ability to enhance both normal and impaired memory performance (Licinio and Wong, 2002; Alonso et al., 2002a). BDNF levels decrease after chronic stress circumstances, where BDNF establishes a connection between stress and mood disorders, as well as somatic ailments (Bulygina et al., 2011). The expression of BDNF was shown to be controlled by chronic stress (Filho et al., 2015). BDNF, also plays a vital role in facilitating the neural processes that are responsible for learning and memory (Marosi

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and Mattson, 2014). The level of its expression is increased in the hippocampus of animals that perform a spatial memory task, and decreasing its expression leads to difficulties in spatial learning and memory (Bekinschtein et al., 2014). We previously showed a significant decrease in hippocampal BDNF levels along with a decline in spatial learning and memory following extended exposure to stress (Alzoubi et al., 2020), which is consistent with earlier findings (Bulygina et al., 2011; Filho et al., 2015).

Oxidative stress describes the imbalance between reactive oxygen species and the antioxidant opposing forces (Gupta et al., 2003). Oxidative stress in the brain is associated with neuronal damage and subsequential learning and memory (Fukui et al., 2002; Jhoo et al., 2004). Additionally, increased brain oxidative stress has a vital role in cognitive impairment caused by normal aging and neurodegenerative diseases. Hence, administration of antioxidant agents has been shown to improve such deficits (Alzoubi et al., 2018; Rababa'h et al., 2018; Alzoubi et al., 2017).

Sildenafil citrate is a widely used oral therapy for erectile dysfunction. It is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE) type 5 in corpora cavernosa (Shafiei et al., 2006). Several studies have reported sildenafil enhances cognitive function in normal animals (Fukui et al., 2002; Jhoo et al., 2004; Rababa'h et al., 2018; Alzoubi et al., 2017). It has also been reported that sildenafil improves object recognition memory in rats (Prickaerts et al., 2005a; Rutten et al., 2008; Boccia et al., 2011). Moreover, it has been shown that sildenafil modulates memory impairment associated with diabetes and electroconvulsive shock (Patil et al., 2006), cerebral hypo-perfusion (Dias Fiuza et al., 2013), Alzheimer's disease (Cuadrado-Tejedor et al., 2011a; Orejana et al., 2012), and schizophrenia (Goff et al., 2009). Several studies are now focusing on the role of PDEs in the central nervous system (CNS) and the potential use of PDE inhibitors for nervous system disorders. This can be explained by the presence of PDEs in different regions of the CNS (D'Sa et al., 2002; Suvarna and O'Donnell, 2002; van et al., 2002; Houslay and Adams, 2003; Pitts et al., 2004; Reyes-et al., 2005), and to the fact that cAMP and cGMP have been recognized as secondary messengers of several neuronal phenomena, such as synaptic plasticity (Barnstable et al., 2004; Feil et al., 2005; Makhinson et al., 2006; Liu et al., 2007; Wu et al., 2007). On the other hand, sildenafil was shown to possess oxidative stress-protective properties (Guzman et al., 2011; Puerta et al., 2012). In the current study, we investigated the possible beneficial effect of sildenafil in preventing memory impairment induced by chronic stress using the radial arm water maze (RAWM) behavioral study to determine the effect of chronic administration of sildenafil citrate on learning and memory impairment associated with chronic psychosocial stress.

2. Methods

Adult male Wistar rats, with a starting weight of 200–250 g (8–10 weeks of age), were used in the study. The animals were housed in plastic cages (55X45 × 25 cm), with 5 rats in each, with wood shaving as bedding, during a 12-h light/dark cycle (light at 7:00 a.m.). The experimental animals were maintained at room temperature under hygienic conditions, with free access to food and water. All experimental procedures were performed during the light cycle, approved by the Animal Care Use Committee (ACUC), and adopted by the Jordan University of Science and Technology.

2.1. Animal groups and treatments

The rats were assigned randomly into four groups (n = 15/group): Control (where rats were given 1 ml/kg distilled water daily intraperitoneally (i.p.) as a vehicle treatment); Stress (rats were given 1 ml/kg distilled water daily i.p. as a vehicle treatment, simultaneously rats were subjected to stress using intruder model); Sildenafil (rats were given a daily dose of 3 mg/kg sildenafil citrate i.p, Hikma Pharmaceutical, Amman, Jordan), and Stress plus Sildenafil (rats were given a daily dose of 3 mg/kg sildenafil citrate i.p. simultaneously rats were subjected to stress using intruder model). This dose for sildenafil was based on previous animal studies, which showed neuroprotective effects in conditions other than chronic stress (Rutten et al., 2005; Devan et al., 2006; Rodefer et al., 2012). Animals were allowed to acclimatize for three weeks before experimental manipulation began, and then each group was randomly divided into two different cages. All manipulations started on day 1 of the two-month treatment and continued throughout the days of behavioral tests.

Sildenafil citrate solution at a concentration of 3 mg/mL was prepared daily by dissolving 45 mg of sildenafil citrate powder in distilled water to a final volume of 15 ml and shaking with a vortex until a clear solution was formed (Rutten et al., 2005; Devan et al., 2006; Rodefer et al., 2012). The rats were weighed every three days to ensure a proper weight-dependent dose for each rat.

2.2. Induction of chronic psychosocial stress

Stress was induced by using the intruder model as previously described (Gerges et al., 2001). Two groups of animals were housed in two cages (n = 5/cage). Stress was generated by daily random switching of two animals from one cage to the other for 8 weeks. This model of stress, termed "intruder psychosocial stress," produces stress by disrupting established social hierarchy such that rats must continuously adjust to new situations. Stress was detected by increased serum corticosterone levels (Gerges et al., 2001) and elevation of blood pressure (Alkadhi et al., 2005).

2.3. The radial arm water maze (RAWM) procedure

After eight weeks of stress and/or sildenafil treatment, all four groups were tested for spatial learning and memory performance in the RAWM. The RAWM consists of a black circular tub filled with water, with six V-shaped stainless-steel plates arranged to form a swimming field of 6 arms connected at a central area. The water temperature was maintained at 24 ±1C°. A black platform hidden 2 cm below the water level was placed at the end of one of the six arms (the goal arm). Starting from any arm other than the goal arm, the rat must find the submerged platform by swimming to the end of the goal arm. In a particular trial, the rat was allowed to swim for 1 min to locate the submerged platform. A trial ended when the rat located the submerged platform, where it was allowed to stay 15 s on the platform before the subsequent trial began in a different start arm. If the rat did not find the submerged platform in the goal arm after 1 min, the experimenter would guide the rat to the goal arm and allow it to stay on the platform for 15 s before removal to begin the subsequent trial. An error was registered when the rat entered an arm other than the goal arm, which is the entry of the entire rat body, including the tail. Each rat was allowed six consecutive trials (acquisition phase), followed by short-term memory tests 30 min later, then by long-term memory tests 5 h and 24 h after the acquisition phase. The learning trials and memory tests did not change the goal arm for a particular rat. All the experiments were done in a dimly lit room, using 2 pictures placed in a fixed position on the walls as visual cues for the animals.

2.4. Hippocampus dissection and homogenization

The rats were decapitated, and the brain was removed immediately from the skull and placed on a filter paper soaked with normal saline over a Petri dish filled with crushed ice. Each of the right and left hippocampus was immediately dissected and extended gently over the filter paper and divided into two parts, the anterior part of the right hippocampus was placed with the posterior part of the left hippocampus in a pre-labeled Eppendorf tube, and vice versa, and immediately moved to liquid nitrogen, until finally frozen at −20C° to the time of tissue

analysis.

Homogenization of hippocampal tissues was done using a plastic pestle in 600 μL phosphate buffer saline (8 g NaCl, 0.2 g KCl, 0.24 g KH2PO4, and 1.44 g Na2HPO4, 5 mM EDTA) with the addition of protease inhibitor cocktail (Sigma-Aldrich Corp, USA). Then, the homogenized tissues were centrifuged at 15,000×*g* for 10 min at 4C^{o} to remove the insoluble materials; then, the supernatant was taken and divided into 4 aliquots and stored. Total protein concentration was measured using BioRAD procedure (Hercules, CA, USA).

2.5. Molecular assays

The hippocampal levels of brain neuroprotective and oxidative stress parameters were assessed in all experimental groups. The following biomarkers were evaluated: brain-derived neurotrophic factor (BDNF; DouSet ELISA Development System, R&D system, USA), superoxide dismutase (SOD; Sigma-Aldrich Corp., MI, USA), catalase (Cayman Chem, Ann Arbor, MI, USA), glutathione peroxidase (GPx; Sigma-Aldrich, MI, USA), reduced glutathione (GSH; Sigma-Aldrich Corp., MI, USA), oxidized glutathione (GSSG; Sigma-Aldrich Corp., MI, USA), GSH/GSSG, and thiobarbituric acid reactive substances (TBARS; Cayman Chem. Com. Ann Arbor, MI, USA). These biomarkers were assessed using the ELISA standard technique following the commercially available kit instructions. The level was assessed following all procedures at the kits' specified wavelength using an automated plate reader (ELx800, Bio-tek instrument, plate Reader Highland Park, Winooski, USA).

2.6. Statistical analysis

All statistics were carried out using the GraphPad Prism (4.0) computer program. The errors were compared using two-way ANOVA, followed by Bonferroni post-test. The independent variables were time (repeated measures factor) and treatment (between-subjects factor) groups. Immunoassay results were compared using one-way ANOVA, followed by the Bonferroni post-test. $P < 0.05$ was considered significant. All values are represented as mean ± SEM.

3. Results

Learning and memory tests using RAWM were performed directly at the end of the treatment course. At the beginning of the experiment, rats in all groups made a higher number of errors. The number of errors decreased as the animals had more training trials, with no significant difference among all study groups in all learning trials (Fig. 1). On the other hand, memory tests of the RAWM showed that stress impaired short-term memory (30 min) with no significant effect on long-term memory (5 h and 24 h). In the short-term memory test, the number of errors made by stressed rats was significantly higher than those in the control, sildenafil, and stress plus sildenafil groups (F(Bailey et al., 1996; Srivareerat et al., 2009) = 11.16, $p < 0.01$). Moreover, the errors in the control, sildenafil, and stress plus sildenafil groups were comparable. Hence, sildenafil prevented the effect of stress on short-term memory (Fig. 1). Sildenafil administration to normal rats showed no changes in errors in all memory tests in RAWM compared to the control group. Thus, sildenafil prevented short-term memory impairment caused by stress; however, it did not improve cognitive performance in normal animals.

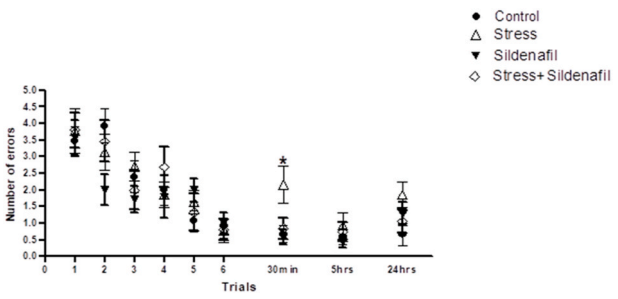

Fig. 1. RAWM performance. Comparisons were made using two-way ANOVA, followed by the Bonferroni post-test. $P < 0.05$ was considered significant. Each column indicates the mean ± SEM. * indicates significant differences compared to all other groups ($P<0.05$).

Fig. 2 shows the comparison of the hippocampal BDNF levels among all tested groups. The current results revealed a negative impact of stress on the BDNF level compared to the control group, and this effect was prevented by sildenafil (F(Bailey et al., 1996; Smith et al., 1995) = 7.49, $p < 0.01$). No significant effect on the hippocampal BDNF level was observed when sildenafil was administered to normal rats.

The current study showed that no significant differences were observed in the hippocampal SOD, catalase, GPx, and TBARS levels between the stress and the sildenafil-treated groups compared to the control SOD: F (Bailey et al., 1996; Rasmusson et al., 2002) = 0.22, $p > 0.05$, catalase: F (Bailey et al., 1996; Smith, 1996) = 0.15, $p > 0.05$, GPx: F (Bailey et al., 1996; Lu, 2003) = 0.20, $p > 0.05$, TBARS: F (Bailey et al., 1996; Aleisa et al., 2006a) = 0.15, $p > 0.05$; Fig. 3(A-D respectively). Moreover, there was no significant alteration in the level of reduced glutathione (GSH) between the stress and the sildenafil-treated groups compared to the control (F(Bailey et al., 1996; Rasmusson et al., 2002) = 0.66, $p > 0.05$; Fig. 4A). However, a significant increase in the level of oxidized glutathione was observed in the stress group (F (Bailey et al., 1996; Aleisa et al., 2006a) = 4.2, $p < 0.05$; Fig. 4B), while the administration of sildenafil prevented this change. No significant changes in GSSG levels were observed when sildenafil was administered for normal rats compared to the control group.

4. Discussion

The current study showed that chronic psychosocial stress impaired short-term memory without affecting long-term memory. This came in consistent with the findings of previous studies (Gerges et al., 2004; Rababa'h et al., 2019b). Moreover, the present work revealed that stress reduces basal protein levels of hippocampal BDNF, which agrees with the results declared by Xu et al., (2004), who reported a reduction in the levels of BDNF following repeated restraint stress.

The decreased BDNF level was also reported after chronic psychosocial stress and was normalized by chronic nicotine treatment (Aleisa et al., 2006a). The reduction of BDNF basal levels during chronic stress may be due to the reported reduction in the expression of BDNF in the hippocampus (Smith, 1996; Smith et al., 1995). The reduced neurotrophic factors such as BDNF during stress may exaggerate the stress-induced excitotoxicity. Additionally, stress-induced down--regulation of hippocampal BDNF expression was observed after physical

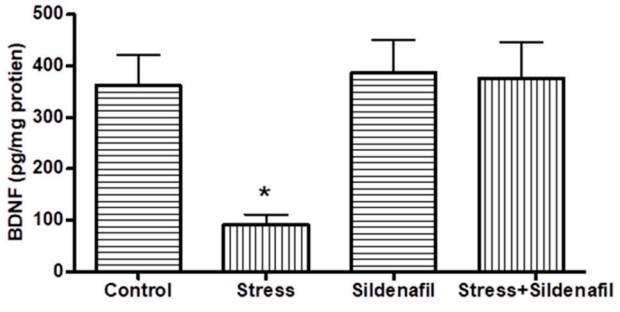

Fig. 2. Hippocampal BDNF levels. Comparison of control, stress, sildenafil, and stress + sildenafil groups. Comparisons were made using one-way ANOVA, followed by the Bonferroni post-test. $P < 0.05$ was considered significant. Each column indicates the mean ± SEM. * indicate significant differences compared to all other groups.

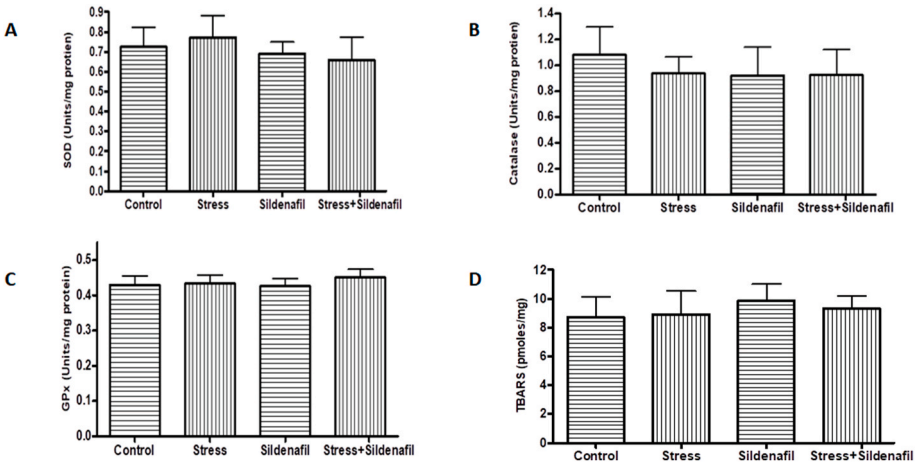

Fig. 3. Alterations in the hippocampal antioxidant biomarkers among different treated groups. Comparison of control, stress, sildenafil, and stress + sildenafil groups. (A) levels of superoxide dismutase (SOD), (B) levels of catalase, and (C) Levels of glutathione peroxidase (GPx). Each point is the mean ± SEM.

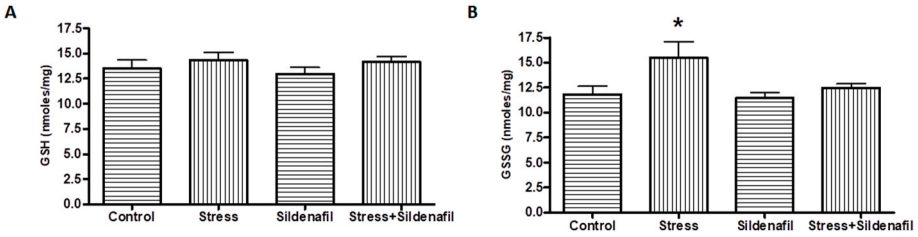

Fig. 4. Alterations in glutathione levels in the hippocampus. Comparison of control, stress, sildenafil, and stress + sildenafil groups. (A) Levels of reduced glutathione (GSH), and (B) levels of oxidized glutathione (GSSG). Each point is the mean ± SEM. * Indicate significant difference ($P < 0.05$) from control group.

and psychological stress (Rasmusson et al., 2002). Since BDNF mRNA transcription and BDNF secretion are activity-dependent processes and increased markedly during long-term potentiation (LTP) (Lu, 2003). The reduced hippocampal BDNF levels in stressed rats could be explained by impaired synaptic plasticity induced by chronic stress (Alkadhi, 2011; Srivareerat et al., 2009). Moreover, the reduced hippocampal BDNF level can contribute to the short-term memory impairment associated with chronic psychosocial stress (Alonso et al., 2002b).

Several studies have shown that physical and/or psychological stress induces oxidative stress and decreases the antioxidant level. Total antioxidant levels significantly decline in the acute cold restraint stress group as compared with the control group, with insignificant changes in the chronic stress groups (Zaidi et al., 2005; Abdel- and Sater, 2012). On the other hand, *Radak* et al. suggested that limb immobilization induces oxidative damage to the hippocampus, and this damage results in impairment of cognitive function (Radak et al., 2001). Furthermore, *Zaidi and colleagues* showed that immobilization of rats generated oxidative stress in the rat brain by reducing the activities of SOD, glutathione-S-transferase (GST), and glutathione and increasing the lipid peroxidation (Zaidi and Banu, 2004). This study showed that two months of psychological stress using the intruder model did not markedly affect the oxidative stress markers (SOD, catalase, GPx, GSH, and TBARS) in the hippocampus, with the exception of the level of the oxidized form of glutathione (GSSG) which was significantly elevated in the stressed rats compared to the control group (Zaidi and Banu, 2004). Hence, comparing the current results with previous studies suggests that the nature and duration of the stress are critical factors in determining the extent of oxidative damage.

Prickaerts and colleagues were the first to describe the memory-enhancing effects of phosphodiesterase (PDE) inhibition using the PDE5 inhibitor zaprinast (Prickaerts et al., 1997). However, zaprinast is not selective for PDE5 and inhibits PDE1, 9, 10, and 11 (Bender and Beavo, 2006). So far, several studies have shown the positive effects of PDE5 inhibitors on memory performance in the object recognition task in adult rats; zaprinast (Prickaerts et al., 1997; Domek-Łopacińska and Strosznajder, 2008), sildenafil (Prickaerts et al., 2002, 2005b), and vardenafil (Prickaerts et al., 2002; Rutten et al., 2007) improved memory consolidation. In addition, *Rutten* et al. showed that sildenafil improved memory consolidation in mice in this task (Rutten et al., 2005). Several studies have shown spatial memory improvement in an adapted version of the elevated plus-maze in rodents (Singh and Parle, 2003; Zuccarello et al., 2020) after treatment with PDE5 inhibitors.

Most of the studies to date have evaluated the effect of acute systemic treatment of PDE5 inhibitors on cognitive processes, and it is not known whether chronic treatment has such an effect. The current study showed that administration of 3 mg/kg sildenafil intraperitoneally for two months did not improve or impair learning and memory performance in RAWM when given to normal rats compared to the control group. The effect of sildenafil citrate on hippocampal BDNF levels was investigated in some disease models. One study reported that BDNF levels were reduced in the hippocampus of Tg 2576 saline-treated mice (a model of Alzheimer's disease), and this reduction was ameliorated by sildenafil treatment (Cuadrado-Tejedor et al., 2011b). Sildenafil normalized BDNF levels in diabetic mice (Puerta et al., 2010) and protected against 3-nitro propionic acid neurotoxicity through the modulation of BDNF expression (Puerta et al., 2010). This study showed that administering sildenafil to normal rats did not significantly affect the hippocampal BDNF level compared to the control rats. The effect of sildenafil on hippocampal BDNF level could be due to enhancement in the synaptic plasticity and LTP through the retrograde nitric oxide signaling in a glutamatergic synapse (Feil and Kleppisch, 2008). This study showed that administering sildenafil to normal rats has no effect on oxidative stress markers compared to the control group. These results agree with Uthayathas et al. (2013), who concluded that glutathione content,

catalase activity, superoxide dismutase, and glutathione peroxidase were not significantly altered by sildenafil treatment. On the other hand, other studies showed that PDE5 inhibitors protect against oxidative stress (Arafa and Atteia, 2013; Guzmán et al., 2011; Perk et al., 2008). However, these studies evaluated the antioxidant effect of a single dose of PDE5 inhibitors, which suggests that the antioxidant effect of PDE5 inhibitors is time-dependent and relies on the origin of the samples analyzed.

The current work revealed that chronic psychological stress induced in rats using the intruder model impaired only short-term memory but did not affect long-term memory, which correlates with several previous studies (Alzoubi et al., 2009; Alzoubi et al., 2020; Rababa'h et al., 2019b; Aleisa et al., 2006b). This impairment was associated with a significant reduction in the level of BDNF with no significant effect on hippocampal oxidative stress markers. This also correlates to a previous report with the intruder model of chronic stress (Alzoubi et al., 2020). This short-term memory impairment could result from a decrease in many molecules involved in synaptic plasticity, including reductions in the BDNF mRNA and protein levels. However, the exact mechanism for the differential impairment of short-term but not long-term hippocampus memory during chronic stress is unknown and needs further investigation.

Sildenafil administration normalized short-term memory impairment and reduced BDNF levels associated with chronic psychological stress. Stressed rats treated with sildenafil showed fewer errors than stressed rats without any treatment; hence, the protective effect of sildenafil in stressed rats was associated with normalizing the level of hippocampal BDNF. Sildenafil's ability to prevent short-term memory impairment could be due to its ability to enhance synaptic plasticity via retrograde NO signaling in a glutamatergic synapse, increasing BDNF level. This suggested mechanism by which sildenafil normalizes BDNF levels needs further investigation. Finally, this study only investigated male rats; future works should include female rats to increase the inclusivity of this research.

5. Conclusions

In conclusion, chronic psychosocial stress-induced short-term memory impairment, and the chronic administration of sildenafil citrate prevented this impairment, possibly by normalizing the level of BDNF. Interestingly, chronic administration of sildenafil to normal rats neither improved learning and memory performance in RAWM nor affected the BDNF level or oxidative stress markers, suggesting that sildenafil corrects the impairment in memory and normalizes the BDNF level only in stressed animals.

Human and animal rights

The study was approved by the Animal Use and Care Committee and the Deanship of Research Committee at JUST (approval number: 2012/207).

Consent for publication

Not applicable.

Availability of data and materials

Data will be available upon request via e-mailing the corresponding author.

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CRediT authorship contribution statement

Tareq I. Jibril: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Karem H. Alzoubi:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nizar M. Mhaidat:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Writing – original draft, Writing – review & editing. **Omar F. Khabour:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Mohammad A.Y. Alqudah:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Abeer M. Rababa'h:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Nasr Alrabadi:** Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **Doaa Al-udatt:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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