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The Effects of Oxytocin on Cognitive Defect Caused by Chronic Restraint Stress Applied to Adolescent Rats and on Hippocampal VEGF and BDNF Levels

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Manuscript Preparation E
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Background: Because brain development continues during adolescence, the effects of chronic stress on hippocampal changes that occur during that period are permanent. Oxytocin, which is synthesized in the hypothalamus and has many receptors in brain regions, including the hippocampus, may affect learning-memory. This study aimed to investigate chronic restraint stress on hippocampal functions, and hippocampal vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) levels in adolescent male and female rats and the role of oxytocin in these effects.

Material/Methods: Experimental groups included control, stress+oxytocin, and stress+saline groups. Restraint stress was applied to all the stress groups for 1 h/day, for 7 days. Learning-memory tests were performed after the 7th day.

Results: In the stress+oxytocin groups, the process of finding the platform was shorter than in others groups. The stress+saline groups spent less time, whereas the stress+oxytocin groups spent more time, on the target quadrant in the probe trial. In the stress+oxytocin groups thigmotaxis time (indicating anxiety) decreased, but VEGF and BDNF levels increased. A positive correlation was found between VEGF and BDNF levels and the time spent within the target quadrant.

Conclusions: The results indicate that impaired hippocampal learning and memory loss due to chronic restraint stress can be positively affected by intranasal oxytocin.

MeSH Keywords: Adolescent • Brain-Derived Neurotrophic Factor • Learning • Oxytocin • Stress, Psychological • Vascular Endothelial Growth Factors

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Background

Stress is a well known environmental factor that can affect human and animals, resulting in behavioral changes and causing various diseases. In addition, stress is acknowledged as a critical regulator in brain functions and cognition. The hippocampus, which is very susceptible to stress, is the one of the most important regions in the brain, and is responsible for learning and memory [1]. Therefore, when responding to stress, the hippocampus has a significant function in the negative feedback regulation of glucocorticoid release from the HPA axis [2]. Glucocorticoids affect cognitive functions through neural plasticity, and the receptors in the hippocampus mediate these tasks in that region. As a consequence, the structure and function of the hippocampus are easily impacted by chronic stress factors [3]. Studies indicate that prolonged and/or recurrent stress can negatively influence learning and memory in adults [4]. On the other hand, such effects are temporary and can regress when stress is eliminated [5]. The effects of chronic stress in the adolescent period are permanent because brain development and maturation of the HPA have not yet been completed [6].

The adolescent period in rats begins between the 28th and 42nd days after birth and continues until the 60th day [7]. The rodent hippocampus develops and its volume increases throughout the period of adolescence [8]. Compared to adults, the hippocampal cell proliferation rate is higher in adolescents and dendritic intensity is at maximum in puberty [9]. Simultaneously, compared to the other ages, daily vital stresses are perceived as higher and cause developmental changes by activating various neural systems [10].

In mammalians, oxytocin is important in neuromodulation and neurotransmission in the central nervous system (CNS) [11]. Paraventricular oxytocinergic neurons provide projections to various brain regions like the hippocampus and the amygdale [12]. In humans, it was shown that oxytocin can influence behavior by affecting the CNS and it is released by social interaction, touching, and coitus [13]. In laboratory animals, it was shown that oxytocin, which normally cannot pass through the blood-brain barrier, can pass through it when applied intranasally [11,13]. In addition, oxytocin injections decreased stress response and anxiety [14]. Studies have shown that oxytocin plays a critical role in both learning and memory [15]. Nevertheless, the effect of oxytocin on impaired memory functions related to chronic stress is not yet known.

Angiotrophic and neurotrophic factors (NTF) play a critical role in neuronal lifecycle, differentiation, and synaptic plasticity. There is a relationship between neurotrophic and angiogenic factors based on brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) which has been suggested as a model for adult neurogenesis [16]. BDNF has been proposed as a trophic factor that can alleviate damage to the hippocampus induced by stress [17]. It has been found that BDNF injections in the dentate gyrus and CA3 areas can improve performance on behavioral tests [18]. Studies incorporating single or repeated stress treatments have reported results of decreased BDNF mRNA throughout the hippocampal region [19]. In addition, VEGF has direct neurotrophic and neuroprotective consequences [16]. VEGF receptors are found on endothelial and nonvascular cells, including neurons, where it is believed they are responsible for the regulation of neural development [20]. It is apparent that stress affects both VEGF and BDNF levels in the adult hippocampus. The levels of both of these factors are decreased by chronic stress but the way in which this transpires is unknown [21]. However, in adolescents the impacts of stress on hippocampal VEGF and BDNF levels are unknown. This study aimed to investigate chronic restraint stress on hippocampal functions, and hippocampal VEGF and BDNF levels in adolescent male and female rats and the role of oxytocin in these effects.

Material and Methods

Subjects

Forty-two 31-day-old Wistar Albino rats were used in the study (the adolescent period is postnatal days (PND) 28–42). Between 09:00 and 11:00 am, experiments were conducted in a sound-attenuated and air-regulated experimental room. Standard colony conditions of a 12 h light/dark cycle (lights on at 07:00 am), constant room temperature (22±1°C), and humidity (60%) were maintained. Food and water were available constantly. The experiments were performed in accordance with the guidelines provided by the Experimental Animal Laboratory, and approved by the Animal Care and Use Committee of the Dokuz Eylül University School of Medicine.

Experimental groups

The experimental animals were divided into 6 groups: Group 1: control males, Group 2: control females, Group 3: stress+oxytocin males, Group 4: stress+oxytocin females, Group 5: stress+saline males, Group 6: stress+saline females (for each group n=7; 42 rats in total). The experimental groups (stress+oxytocin and stress+saline) were subjected to chronic restraint stress (1 h per day, 7 consecutive days). The control groups were not subjected to stress.

Restraint stress protocol

The rats' trunks were wrapped with a restrictive harness and they were placed on a wooden plate for a period of 60 min.

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The animals could move only their head and limbs but not their trunk. This method of restraint stress has been used in other studies of physical and psychogenic stress models in rodents [22]. Following the completion of the restraint stress, a 100-µl pipette was used to administer intranasal 2 µg/kg oxytocin or saline [23]. The oxytocin (for the stress+oxytocin groups) or saline (for the stress+saline groups) was administered to both the left and right rhinarium equally and gradually by insertion of the tip of the pipette. The rats were returned to their home cage upon completion of the application. At least 2 days prior to the experiment, rats were held for a 2-min period to reduce non-specific stress responses that might occur during the administration procedure. Upon completion of the 7-day stress period, all rats were subjected to learning and memory tests for evaluation of hippocampal function.

Learning and memory test

The Morris water maze (MWM) was used to evaluate learning and memory. A round black Plexiglas pool with a diameter of 140 cm and a height of 75 cm was filled with warm water (22±1°C). A platform with an 11-cm diameter was placed 1.5 cm below the water surface in the pool. All groups received 5 daily trials for 4 days with the intention to train the rats concerning the position of the platform. On each of the 4 days, a different initiation point (north, south, east, west) was chosen and the same point was used for the whole day. The location of the platform was not changed for the duration of the experiment. It was expected that the rats find the platform within 60 s of being placed in the water and they were allowed to remain on the platform for a period of 20 s. The time it took for the rats to reach the platform, the swimming speeds, and the distances they covered within the 4-day learning process were calculated and then evaluated. On the fifth and final day, the platform was removed and a probe trial was conducted. Then the duration the rats spent on the target quadrant, which had previously been hidden by the platform, and on the opposite quadrant, were calculated for 60 s. The results of the rats swimming around the pool wall at a distance of 15 cm in the probe trial was indicative of anxiety and therefore evaluated as thigmotaxis. An HVS image video tracking system (Buckingham, UK) was used to record and analyze the results of the learning tests.

Biochemical analysis

Following the MWM test, the rats were sacrificed using light ether anesthesia, blood was drawn, and the brains were removed. Commercially available ELISA kits specific for rat (BDNF Catalog Number EK0308, Boster Immunoleader, Wuhan, China with assay sensitivity <2 pg/ml and range 31.2–2000 pg/ml) were used to determine the BDNF and VEGF levels. In compliance with the manufacturer's instructions, the hippocampus homogenates were measured using VEGF catalog no. EK0308, Boster Immunoleader, Wuhan, China, with assay sensitivity <1 pg/ml and range 15.6–1000 pg/ml).

Statistical analysis

SPSS 15.0 was used to complete the statistical analysis and the differences in the behavioral and biochemical parameters were evaluated according to the ANOVA post hoc Sheefe comparisons. The GLM repeated measure was used to determine the differences between the learning periods in the MWM. Pearson correlation analysis was conducted and a correlation between the MWM test results and BDNF, VEGF, and ELISA results was obtained. The results are presented as mean ±S.E.M. (the significance level was set at $p \leq 0.05$).

Results

This study results clearly indicate that chronic restraint stress has adverse impacts on the learning process in both genders. The findings show that in the MWM learning test, oxytocin inhibited the process of finding the platform; the duration was prolonged as a result of stress ($p<0.05$ in males and females) (Figure 1A, 1B). In the probe trial (MWM memory test), the groups subjected to stress+saline spent less time in the target quadrant ($p<0.002$ for both sexes) and spent more time in the opposite quadrant ($p<0.05$ for both sexes). However, that time was prolonged with intranasal oxytocin ($p<0.001$ for both sexes) (Figure 2A, 2B). In addition, in the oxytocin-administered groups, thigmotaxis time was shorter ($p<0.001$ for both sexes) (Figure 3), whereas, compared to the other groups, VEGF and BDNF levels were higher (VEGF, $p<0.001$, BDNF, $p<0.05$ in females; VEGF, $p<0.002$, BDNF, $p<0.05$ in males) (Figures 4 and 5). Furthermore, a positive correlation was found between VEGF and BDNF levels and the time on the platform ($r=0.533$, $p=0.002$ with VEGF; $r=0.434$, $p=0.017$ with BDNF).

Discussion

The results of this study indicate that during the MWM learning tests of both female and male rats, the time required to find the hidden platform gradually shortened and reached a stable level. No significant difference between males and females was observed in any of the groups. However, the learning tests of stress+oxytocin and control groups showed that these groups were more successful than the stress+saline groups (Figure 1A, 1B). The probe trial showed that the stress+oxytocin and control groups spent more time within the target quadrant than in the other quadrant, compared to the stress+saline groups (Figure 2A, 2B). Previous studies have shown that stress affects the hippocampus morphology and that increased corticosterone levels suppress cell proliferation

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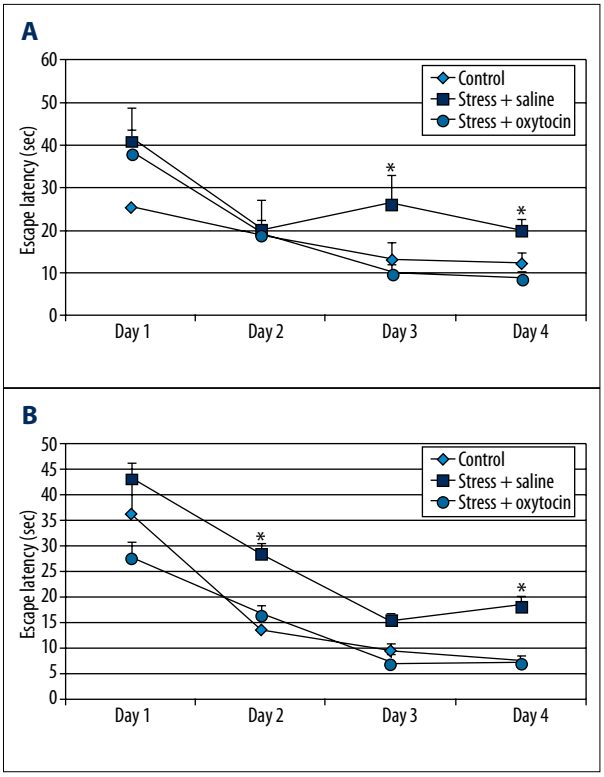


Figure 1. Effects of restraint stress on Morris Water Maze performance. Mean daily latencies to escape from the start point onto the hidden platform (**A**) in the male and (**B**) female rats. * p<0.05 compared to the other groups.

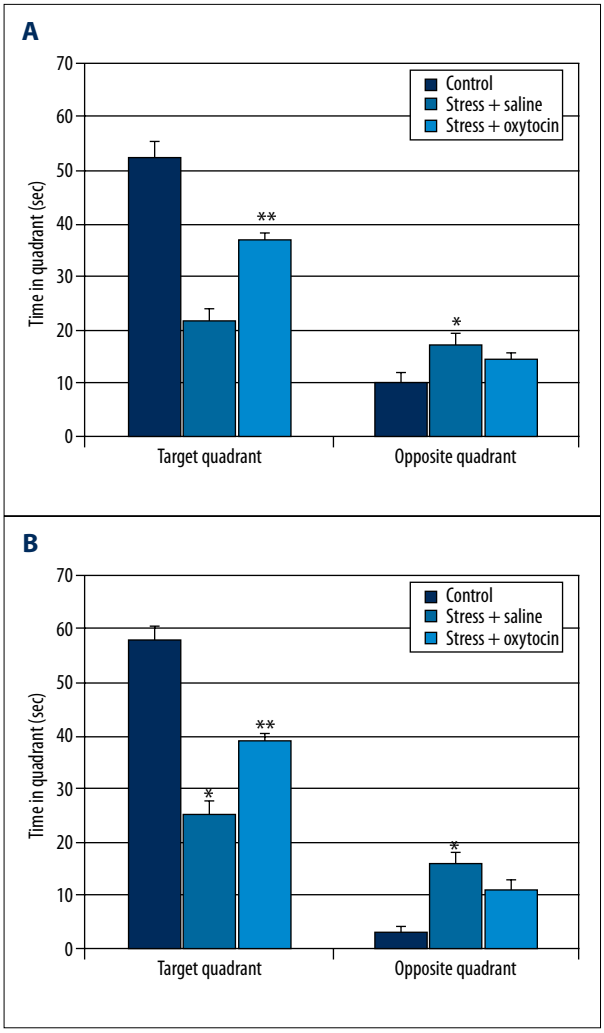


Figure 2. Time spent in the target and opposite quadrant in probe trial. (**A**) in the male and (**B**) female rats. * p<0.002 compared with control groups. ** p<0.001 compared to the stress+saline groups.

and neurogenesis [24]. In rodents stress can cause cell loss in the CA1 and CA3 hippocampal areas [25]. In addition, repeated restraint stress can cause atrophy in the apical dendrites of CA3 pyramidal neurons [26]. Neurons in the hippocampal CA1 and CA3 areas are critically important in establishing the correct route during the learning period and then enabling the subjects to find the hidden platform in the MWM learning test. CA1 neurons in the hippocampus are active in the acquisition of spatial learning and memory [27]. One other undisputed fact is the contribution to long-term potentiation (LTP), which occurs in the CA1 subfield in the hippocampus [28]. The CA1 neurons carry information from the entorhinal cortex or the CA3 subfield, thus enabling learning [29]. The CA3 is connected to the CA1 subfield through the Schaffer collaterals cycle, and the CA1 outputs extend to the subiculum, entorhinal cortex, and prefrontal cortex [30]. Rats with lesions in the hippocampus CA3 subfield, but with a healthy CA1 subfield, could succeed in the learning process in the MWM test. However, in the probe trials, where information needs to be reclaimed, they swam around aimlessly [27]. Therefore, it is clear that having a healthy CA3 and a CA1–CA3 connection is necessary for the function of reference memory. However, the exact involvement of oxytocin in these areas is still very controversial [31]. A significant amount of evidence exists indicating the role of the neuropeptide oxytocin in social interaction [13]. Nevertheless, the influence of oxytocin on the non-social aspects of learning and memory has not been studied sufficiently. A study has shown that during a radial maze task, repeated injections of oxytocin significantly improved long-term memory in virgin female mice. It was suggested that oxytocin injections enhanced consolidation, which is a fundamental trait of hippocampal function [32]. However, within the same experimental setting, oxytocin did not impair short-term memory [15]. A study conducted by Leuner et al. demonstrated that oxytocin increased cell proliferation and neuronal growth in the rats exposed to stress, and protected hippocampal plasticity against the stress hormones [33]. Another study concluded that oxytocin stimulated cell proliferation and neurogenesis by decreasing corticosterone levels [34]. Unfortunately,

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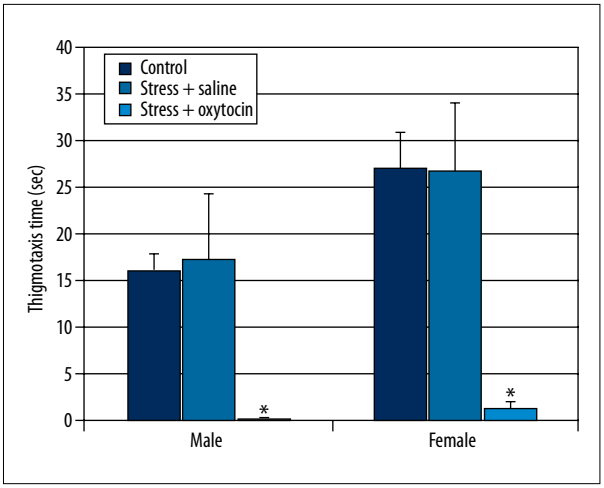


Figure 3. Thigmotaxis time in probe trial in the male and female rats. * p<0.001 compared to the other groups.

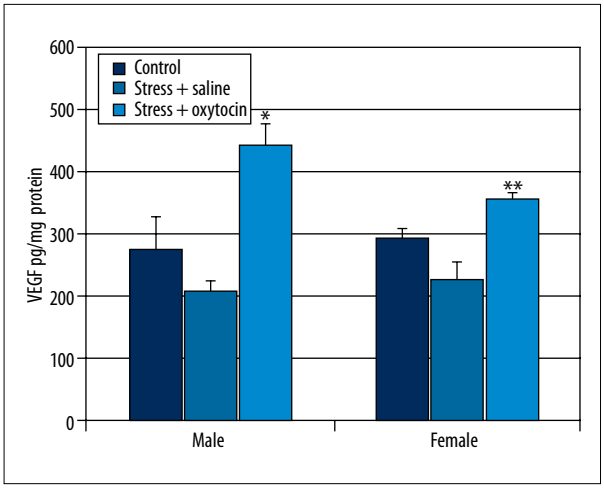


Figure 4. Hippocampal VEGF results. * p<0.002, ** p<0.001 compared to the other groups.

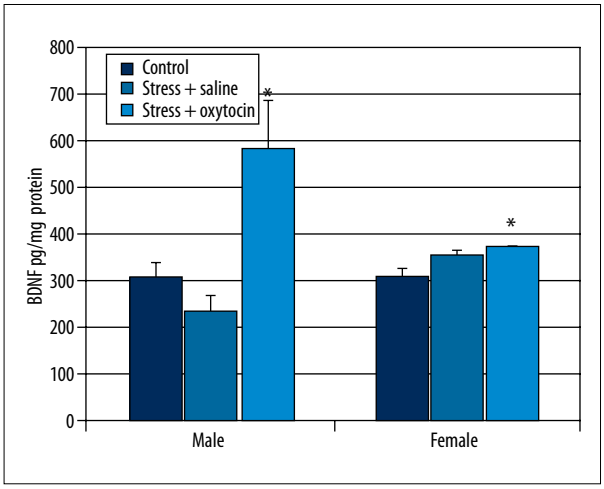


Figure 5. Hippocampal BDNF results. * p<0.05 compared to the other groups.

not enough data is available concerning the effects of oxytocin during the acquisition of learning and in memory tasks.

During the MWM testing in rodents, thigmotaxis was considered to be reliable indicator of anxiety-like behavior. Anxiolytic agents are known to reduce the total duration of thigmotaxis [35]. Conversely, anxiogenic stimuli, such as the systemic administration of corticosteroids, increase thigmotaxis [36]. In our study, the stress+oxytocin groups were more successful than the stress+saline groups in the learning and memory tests. In addition, having a significantly lower thigmotaxis time indicates the decreased anxiety levels in adolescent rats that received oxytocin after being subjected to stress (Figure 3).

NTF are significant factors mediating the growth, development, and plasticity of the brain. Altering NTF levels can impact the brain's normal development and maturation and may cause long-term changes in brain functions and activity. VEGF is an NTF and especially protects hippocampal CA1 cells [37]. Since BDNF is a NTF involved in critical CNS function along with synaptic transmission and plasticity, it has a fundamental role in the survival, maintenance, and growth of neurons [38]. BDNF is known to be widely distributed in the brain, and is synthesized mainly in neurons. The hippocampus and cerebral cortex are responsible for the highest expression [39]. Similarly, BDNF has a crucial function in maintenance of neuron vitality in the central and peripheral nervous systems, as well as the formation of new neurons and synapses [40] and the formation of long-term memory [41]. NTF, such as BDNF and VEGF, are effective in hippocampal learning and are affected by stress. Chronic stress impacts NTF as BDNF and VEGF in the adult hippocampus and influences the process of learning and memory [21]. It was determined that chronic stress and corticosterone administration decreased BDNF levels in the hippocampal dentate gyrus and CA3 regions. Likewise, BDNF injections to these regions have resulted in improvements in learning and memory tests [18]. Also, it was shown that one-time or recurrent physical restraint stress decreased the hippocampal BDNF-mRNA levels [19]. In our study, the BDNF and VEGF levels in adolescent rats were evaluated in the hippocampus, which is the brain region responsible for spatial learning and memory. In the group administered oxytocin immediately after restraint stress, BDNF and VEGF levels were significantly higher (Figures 4 and 5) and there was a positive correlation between the hippocampal VEGF and BDNF levels and the time spent in the target quadrant.

Conclusions

It is not clear how oxytocin affects neurotrophic factors such as VEGF and BDNF. Oxytocin has been shown to play a critical role in the acquisition of learning and memory in animal

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studies. Despite its role in learning and memory indicated in these studies, there is still much to learn about how oxytocin functions at cellular and molecular levels.

When compared to adults, stress in adolescents affects the neural system far more extensively because hippocampal development continues during adolescence. As a result, the female and male adolescent rats exposed to chronic stress experienced inhibitions in hippocampal learning and memory. Furthermore, the hippocampal VEGF and BDNF levels increased and anxiety levels decreased upon the administration of intranasal oxytocin. Our data suggest that in adolescent rats, intranasal oxytocin may positively affect the impaired hippocampal learning and memory resulting from chronic restraint stress. Further studies are required to support and expand this conclusion.

Statement

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Declaration of conflicting interest

The authors declare that there have been no conflicts of interest.

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