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The Effect of Exposure to Noise-Induced Stress during Lactation on Cognitive Behaviors and Synaptic Plasticity in the Hippocampus of Rat Offspring

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ABSTRACT

Background and Objective: The critical period of brain development is the time period between the embryonic period and early life, during which the interaction of genetics and environmental signals leads to the formation of synaptic connections. Exposure to stress during lactation can affect the neurobiological development of offspring. The present study was conducted to investigate the effect of exposure to noise-induced stress during lactation on spatial learning and memory, as well as synaptic plasticity in rat offspring.

Methods: This experimental study was conducted on 4 groups including 10 45-day-old male Wistar rats: control group (CON), and offsprings whose mothers were exposed to noise level of 95 dB for 1 (ST1) or 2 (ST2) or 4 hours (ST4) during the daily lactation. Spatial learning and memory were examined using the Morris water maze test. Basal field excitatory postsynaptic potentials were recorded in the hippocampal CA1 region, and then, long-term potentiation (LTP) was induced by high-frequency stimulation. Serum corticosterone levels of the rats were measured and compared at the end of the study.

Findings: In the ST4 group, the time spent finding the platform increased compared to the CON group ($p<0.001$). Furthermore, the ST4 group (8.91±0.45 seconds) spent less time in the target quadrant compared to the control group (13.23±0.74 seconds) ($p<0.001$). Tetanic stimulation induced LTP in CA1 neurons of the control group (0.9±0.01 mV) and conversely, induced long-term depression (LTD) in the ST4 group (0.5±0.02 mV). Corticosterone in ST4 rats (128.50±4.80 nmol/L) was significantly higher than the control group (97.63±2.90 nmol/L) ($p<0.001$).

Conclusion: The results of this study demonstrated that exposure of lactating rats to noise-induced stress disrupts spatial learning and memory of the offsprings, and leads to synaptic plasticity in hippocampal CA1 region in adulthood by increasing the serum corticosterone levels.

Keywords: *Stress, Lactation, Hippocampus, Spatial Learning, Synaptic Plasticity, Rats.*

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Introduction

Stress is the physiological response of an individual to a stressor, such as a change in environmental conditions; this response is produced by the cooperation of several systems in the mammalian body, the most important of which are the autonomic system and the hypothalamic-pituitary-adrenal (HPA) axis. Although some types of stress are necessary for survival, many of them, especially when chronic, can adversely affect the structure and function of all body systems (1). Exposure to stress as an external factor leads to an increase in plasma levels of corticosterone (2, 3). Corticosterone exerts its effects through glucocorticoid receptors, the presence of which has been proven in various brain regions, especially the hippocampus (4, 5). Existing theories emphasize the importance of two types of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), in memory formation (6).

LTP seems to reflect synaptic mechanisms in memory formation. In fact, LTP is a long-term increase in the strength of synaptic transmission that occurs following high-frequency synaptic activity and has been considered as one of the cellular processes involved in memory storage (6). Evidence suggests that stress, through neuroendocrine changes such as prolonged increases in plasma glucocorticoid levels, impairs LTP induction and facilitates LTD in the hippocampus (7). It has also been shown that exposure to noise-induced stress, in addition to increasing basal corticosterone secretion and impairing spatial memory learning and consolidation and some hematological parameters, has a negative effect on the basal synaptic response recorded from hippocampal CA1 neurons and leads to a decrease in LTP induction in rats (8, 9).

During the critical period of fetus and infant development, the mammalian nervous system is highly influenced by internal and external factors (10). As an external factor, stress can have long-term effects on hippocampal structure and function during infancy (11). It has been shown that the development of granule cells in the DG region of the rat hippocampus begins in late fetal life and continues until the first week after birth (12); thus, exposure to stress in the early postnatal period can alter the structure and development of the hippocampus (13). Previous studies have shown that administration of exogenous corticosterone leads to increased levels of corticosterone in breast milk and the presence of labelled corticosterone in the brain and plasma of the offspring, which indicates that corticosterone can pass breast milk and reach the infant (14).

Stress affects lactation directly by affecting oxytocin and prolactin, thereby inhibiting milk synthesis and secretion, and indirectly by affecting factors such as opioids and neuropeptide Y or maternal behaviors (15, 16). Although maternal stress during lactation does not cause acute activation of the HPA axis in offspring, it does lead to long-term behavioral consequences such as anxiety in rat offspring, similar to those seen when offspring are directly exposed to stress (17). Therefore, it seems that long-term exposure to stress, in addition to affecting maternal care and milk composition, can also affect the neurobiological development of offspring (18). It has been shown that ingestion of a high dose of corticosterone dissolved in drinking water by lactating rats leads to increased corticosterone levels and reduced LTP induction in the hippocampal CA1 region of their 45-day-old offspring (19). The present study was conducted to investigate the effect of exposure to noise-induced stress during lactation on spatial learning and memory and induction of LTP in the hippocampus of rat offspring.

Methods

After approval by the Ethics Committee of Kashan University of Medical Sciences with the code IR.KAUMS.MEDNT.REC.1398.062, this experimental study was conducted on 40 male Wistar rats weighing about 200 to 220 grams and aged 45 days, which were randomly divided into 4 groups of 10. The

mothers of the control group (CO) were kept under standard animal house conditions during lactation, and the mothers of the animals of groups ST1, ST2, and ST4 were exposed to noise-induced stress for 1, 2, and 4 hours per day, respectively, during lactation. At other times, the animals were kept in a standard environment in terms of temperature (22±2°C) and humidity (55±5%) and had free access to water and food. The principles of working with laboratory animals were observed in accordance with the guidelines of the Ethics Committee.

Exposure to noise-induced stress: In order to produce a uniform sound in the environment and to expose the animals to sound from all sides, their cages were placed in a Plexiglas reflective chamber measuring 60×60×90 cm. To expose lactating mothers to urban traffic noise, the sound from traffic in one of the busiest squares in Tehran (Enghelab Square) was first recorded and its intensity was adjusted to 95 dB using Sonar 8.5 software. Then, it was broadcast in the environment through a loudspeaker located 30 cm above the animal cage. In order to ensure that the animals were exposed to the same sound intensity at all times, the sound intensity was monitored throughout the exposure period using a Sound Level Meter (7). Given that the sound recorded from traffic covers a wide range of sound frequencies, only the annoying sound intensity was considered in this study. Lactating rats were exposed to sound every day from 8 AM to 12 noon, when corticosterone secretion is at its lowest (20).

Measuring spatial learning and memory consolidation: The Morris water maze was used for this task. The maze is a water tanker that is hypothetically divided into four equal quadrants: north, south, east, and west, and a rescue platform is placed in the middle of one of these quadrants; it is located about 1.5 cm below the water surface and is not visible from the outside. In the room where the maze is located, there are various spatial signs that are fixed during the experiments and are visible to the animal in the maze. The animal's behavior in the maze is monitored via a camera and analyzed using the "Tracker" version 7.

Learning or training phase: During this phase, the animal was released into the water from one of the four hypothetical sides while facing the wall of the maze and had a maximum of 60 seconds to find the rescue platform. If the animal accidentally found the hidden platform and stood on it, the animal was allowed to stay on the platform for 15 seconds and identify its location by searching the surroundings and seeing the signs in the laboratory. If the rat could not find the platform within the specified time, the animal was slowly guided by the researcher to the platform to find the platform and stand on it for 15 seconds. Then, the animal was removed from the platform and returned to its cage with a towel after drying. After 10 minutes, the experiment was repeated; the difference was that the location of the rat in the maze was different from the previous phase. Each rat had 4 training sessions per day, spaced 10 minutes apart. Overall, this phase of the experiment lasted for 3 days, during which 12 testing sessions were performed on the animals. The mean time required to reach the platform and the distance traveled by the rats in different groups during that time were used to measure spatial learning (21).

Spatial memory retrieval phase or probe: Immediately after completing the 4 learning phases on the third night, the escape platform was removed from the maze and the test was performed. It was necessary to note which of the four parts of the maze the rat (which is usually unable to find the platform) spent the most time in during the test. In this phase of the test, each rat had only 30 seconds to swim in the maze and then it was removed from the maze. The duration of stay and the distance traveled in the correct quadrant of the maze (which had the platform in the previous phase) were used as a measure of recall (21).

Electrophysiology: On the day after the behavioral studies, the rats were anesthetized by intraperitoneal injection of urethane (1.5 g/kg body weight). After the animal's head was fixed in a stereotaxic apparatus (Stoelting, USA), 0.5 ml of 1% lidocaine solution was injected subcutaneously to provide local anesthesia and to separate the scalp from the skull for easy cutting. Then, the scalp was cut from the back of the neck to the area near the nose until the skull was exposed. After determining the bregma, lambda, and midline

regions on the skull, the location of the electrodes was determined using a stereotaxic atlas. The stimulating electrode was placed at coordinates (D=2.4 mm, LR=3.8 mm, AP=-4.2 mm) at the axon of the neurons in the medial entorhinal cortex, and the stabilizing electrode was placed at coordinates (D=2.5 mm, LR=2.5 mm, AP=-3.4 mm) on the dendrites of the neurons in the CA1 region. Both electrodes were bipolar, made of stainless steel with Teflon coating and 0.005-inch diameter (A-M Systems, USA). After the electrodes were placed at the specified locations, the accuracy of the electrode location was checked by applying paired stimulation pulses to achieve greater certainty. The amplitude of the second response being at least 20% higher than the amplitude of the first response indicated the correct location of the stabilizing and stimulating electrodes. In response to the stimulation of entorhinal cortex neurons, excitatory postsynaptic potentials (EPSP) were first amplified by an amplifier (WSI, A3308, Iran) up to 1000 times and then converted into digital data by entering the analog-to-digital converter board (Electromodule 12, ScienceBeam, Iran) and were finally recorded. After about 30 minutes of initial recording of responses and when the response amplitude remained unchanged with constant stimulation intensity, the Input/Output curve was drawn. An intensity of electrical stimulation at which 60% of the maximum response amplitude was obtained was selected as the stimulation intensity for the continuation of the experiment and also for applying tetanic stimulation. Stimulations were applied at a frequency of 0.1 Hz, a duration of 100 microsecond, and a delay of 5 thousandths of a second. Then, EPSP was recorded for 30 minutes. To induce LTP in the tested neuronal circuit, high-frequency tetanic stimulation (HFS) was applied. The pattern of this stimulation consisted of 10 trains of 10 stimuli with a frequency of 200 Hz and an interval of 2 thousandths of a second. The duration of each stimulation pulse was 0.1 thousandth of a second. After tetanic stimulation, the stimulation and recording process continued for 90 minutes. NuroTrace® software (ScienceBeam, Iran) was used for stimulation and recording phenomena and also for response analysis. In order to compare the groups, the percentage change in response amplitude in millivolts was evaluated before and after applying tetanic stimulation. An increase or decrease of at least 20% in response amplitude after tetanic stimulation was considered as the criterion for the occurrence of LTP and LTD, respectively (1, 22).

Serum corticosterone measurement: After the electrophysiology experiments and while the animals were still under deep anesthesia, their heads were cut off using a guillotine and after collecting blood samples from the jugular vein, the samples were first centrifuged at room temperature at 3500 rpm and for subsequent experiments, the blood serum was separated and stored in a -80°C freezer. The level of corticosterone in the animals' serum was examined using an RIA kit (DRG, Germany) and according to the manufacturer's instructions. The level of corticosterone in the animals' serum was measured by a gamma counter (Berthold; LB951G, Germany).

Statistical analysis: The collected data were analyzed using GraphPad Prism version 9 and one-way analysis of variance and Tukey's post-test, and $p<0.05$ was considered significant.

Results

After examining the data related to spatial learning and memory in the study groups using the Morris water maze, and the data related to the time spent and distance traveled to reach the hidden platform in the learning phase, as well as the time spent and distance traveled in the target quadrant in the memory consolidation phase (probe), the following results were obtained. As the learning stages progressed daily, animals in all groups learned the location of the hidden platform and spent less time and distance traveled to find the platform. Data analysis showed that the difference between the control and ST4 groups was statistically significant, and the rats in the ST4 group spent more time finding the hidden platform and traveled more distance ($p<0.001$ for both comparisons) (Figure 1).

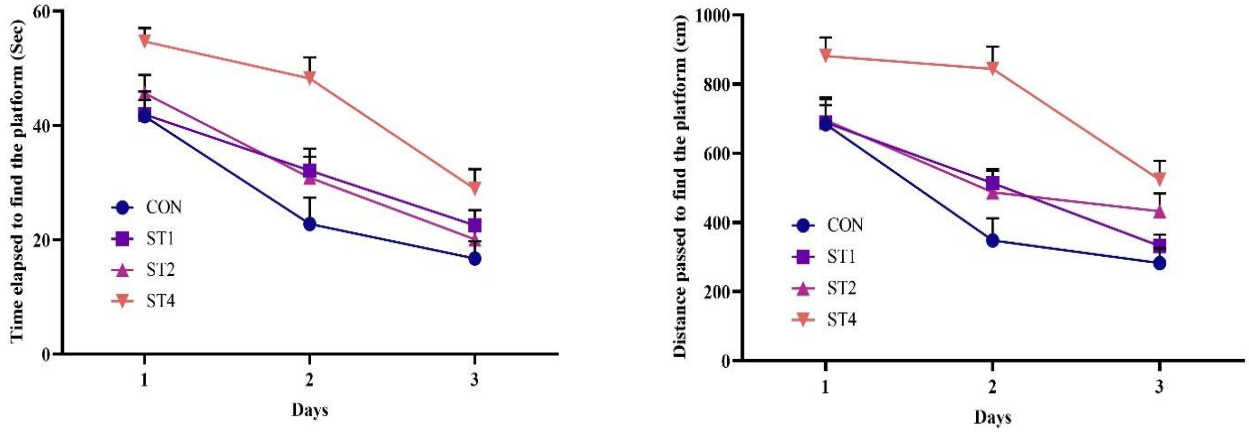

Figure 1. Time spent (left image) and distance traveled (right image) to find the hidden platform by animals in the Morris water maze test on different days of the experiment. The difference between the CON and ST4 groups was significant in both cases (p<0.001). Data are presented as Mean±SD (n=10).

The results of the comparison between groups using the analysis of variance test indicate that in the memory recall phase, the rats in the stress groups spent less time in the target quadrant and traveled less distance compared to the control group, and the longer the time of exposure to stress for their mothers during lactation, the lower these values were (Figure 2). The rats in the control group spent 13.23±0.74 seconds in the target quadrant out of a total of 30 seconds of the probe test, while this time was 8.91±0.45 seconds for the rats in the ST4 group, and this difference was statistically significant (p<0.001). Regarding the distance traveled in the target quadrant, the difference between the control and ST2 (p<0.001) and ST4 groups was also significant (p<0.01).

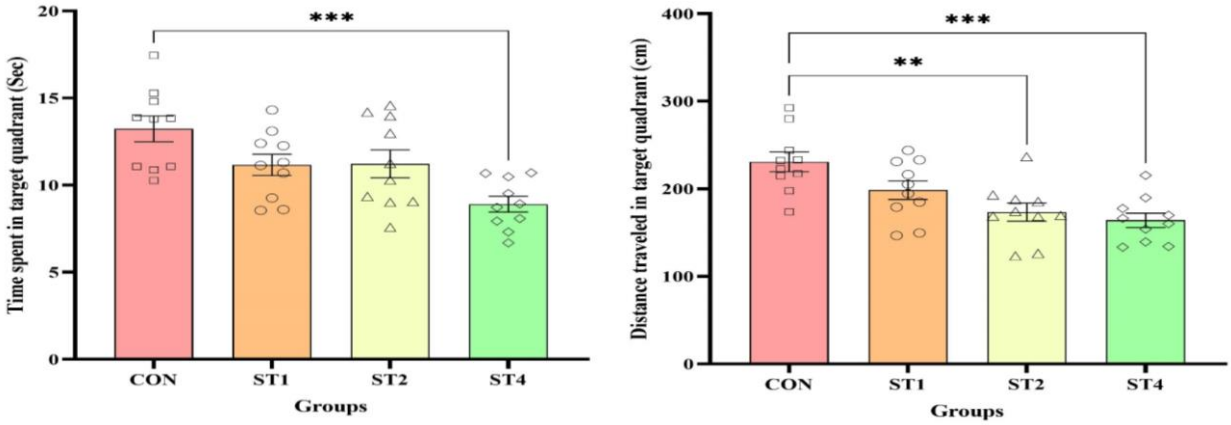

Figure 2. The time spent by the rats in the experimental groups in the information retrieval phase (left image) and the distance they traveled (right image) to find the hidden platform. **The difference between the CON and ST2 groups is significant (p<0.01), ***The difference between the CON and ST4 groups is significant (p<0.001). Data are presented as Mean±SD (n=10).

Data related to responses recorded in the hippocampal CA1 region of rats whose mothers had undergone a standard breastfeeding period showed that the average amplitude of baseline responses in them was 0.86±0.05 mV, while exposure of the lactating mother to stress caused a decrease in the amplitude of baseline responses, and the longer the period of exposure to stress, the more severe this decrease became; the mean amplitude of responses in the ST4 group reached 0.40±0.03 mV, and its difference with the CON group was statistically significant (p<0.0001, Figure 3).

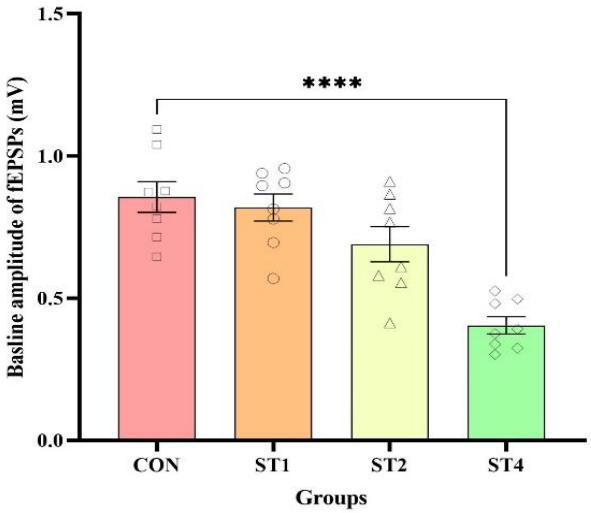

Figure 3. Comparison of mean amplitude of responses in different study groups. ****The difference in amplitude between CON and ST4 groups is significant (p<0.0001). Data are presented as Mean±SD (n=10).**

After recording baseline responses for 30 minutes, LTP was induced in the perforant pathway circuit to the CA1 region by applying tetanic stimulation at a frequency of 200 Hz, and then recording continued for 90 minutes. The results show that LTP induction led to a significant increase in the amplitude of fEPSPs in the CON group, and the difference between pre- and post-LTP induction (an average of 37% increase in amplitude) was significant (p<0.001). As shown in Figure 4, applying tetanic stimulation to the neurons of the hippocampal CA1 region of animals in the stress groups caused the average amplitude change after HFS application in groups ST1, ST2, and ST4 to increase by about 8%, decrease by 1%, and decrease by 23%, respectively; in other words, LTD was induced instead of LTP in group ST4. The results of the statistical test showed that the difference between the amplitude of responses before and after applying tetanic stimulation was significant only in the ST4 group (p<0.001). In addition, there was a statistical difference between the mean amplitude of responses after applying tetanic stimulation between the control group and all three stress groups (p<0.001).

At the end of the experiments, the serum corticosterone level of the animals was examined and it was determined that its mean level in the serum of the animals of the control group was 97.63±2.90 nmol/L, and that the exposure of lactating mothers to stress increased its level in the blood of the offspring; its level in the blood of animals whose mothers were exposed to stress for 4 hours a day during lactation was 128.50±4.80 nmol/L, and its difference with the control group was significant (p<0.0001) (Figure 5).

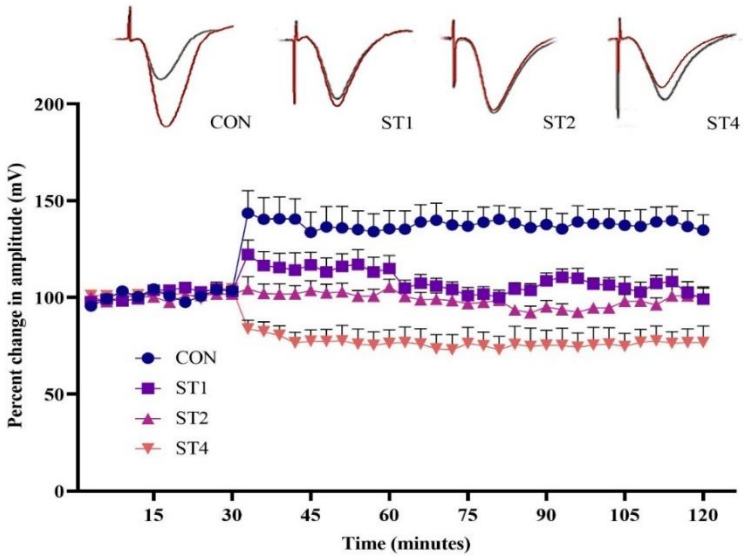

Figure 4. Changes in the amplitude of fEPSPs recorded from the CA1 region of the hippocampus of rats in different experimental groups after applying tetanic stimulation. Recordings obtained before and after HFS induction for different groups. The difference between the amplitude of responses before and after LTP induction in the CON and ST4 groups is significant ($p<0.001$). Also, the difference in the amplitude of responses after LTP induction between the control group and the three stress groups is significant ($p<0.001$). Data are presented as Mean±SD (n=10).

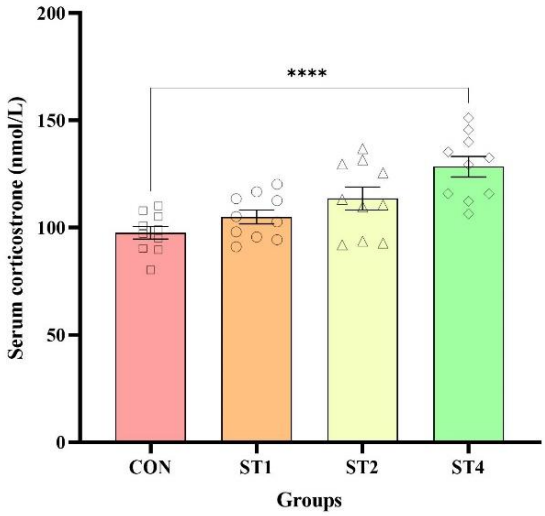

Figure 5. Serum corticosterone levels (nmol/L) of animals in different groups at the end of the study. ****The difference between CON and ST4 groups is significant ($p<0.0001$). Data are presented as Mean±SD (n=10).

Discussion

The present study demonstrated that maternal exposure to noise-induced stress during lactation impairs the spatial learning of their adult offspring in the Morris water maze and they also have problems in spatial memory; in other words, it can be said that their spatial memory is not consolidated. Furthermore, examining the amplitude of postsynaptic field potentials recorded from neurons in the hippocampal CA1 region of their

offspring showed that maternal exposure to stress during lactation for 1, 2, and 4 hours reduces the amplitude of responses in their offspring, which can be considered a type of reduction in neuronal activity. More importantly, the synaptic plasticity of neurons in this region is also impaired, and after tetanic stimulation of neurons in the hippocampal CA1 region, not only is long-term consolidation is absent, but we are even faced with the phenomenon of long-term attenuation. It was also observed that circulating corticosterone was higher than normal in children whose mothers were exposed to noise-induced stress for 4 hours a day, which alone could provide strong evidence for our previous observations.

It has been shown that when lactating mothers are exposed to various types of physical and psychological stress for a long time, plasma corticosterone levels increase in their offspring simultaneously with the activation of the maternal HPA axis; for example, in one study, it was shown that exposure of lactating mothers to physical stress caused an increase in plasma corticosterone in their offspring (from 15.52±7.94 to 38.65±9.31 mg/dL), and the longer the exposure to stress, the more pronounced the increase in plasma corticosterone in the offspring (23). It has also been stated that adding corticosterone to drinking water during lactation leads to a decrease in glucocorticoid receptors type 1 and 2 in the hippocampus of their 30-day-old offspring (24). It has been reported that maternal stress leads to downregulation of GRs in the hippocampus and HPA reactivity, which may be the reasons for changes in stress-induced behavior in the offspring (25).

During the critical period of mammalian brain development, and during the embryonic and early postnatal period, both genetic and environmental factors influence the CNS, and many studies have shown that chronic exposure to any stressor affects the programming and development of the offspring's nervous system (26). Chronic stress and the resulting glucocorticoid elevation have been shown to alter neurochemical activity, excitability, neurogenesis, and even cell death in hippocampal circuits (27). In one study, rats were exposed to restraint stress at 3 weeks of gestation; the density of glucocorticoid receptors (GRs) in the hippocampus of their female offspring was 50% lower than that of unstressed offspring (28). Prolonged deprivation of maternal care as a stressor increases endocrine and behavioral responses to stress (29). In a study, it was shown that these animals display more anxiety-like behaviors in the plasma maze in adulthood (30). On the other hand, a study showed that taking a low dose of corticosterone through drinking water improves learning ability and reduces anxiety and fear behaviors in their offspring (31), although all of these events are disrupted and inhibited in the presence of high levels of corticosterone (18).

Evidence from studies of LTP, learning, and memory suggests that LTP is the major mechanism of memory and learning (32). LTP is a well-known physiological process that is induced by high-frequency stimulation of neural circuits and is a well-accepted laboratory model for changing synaptic activity, or so-called synaptic plasticity (33). In addition, the hippocampal formation, and in particular the CA1 region, with its well-organized neural circuits, is a very suitable site to study this process (34). We found that exposure to stress during lactation leads to suppression of LTP induction and impairment of memory and spatial learning. The results of various studies indicate that there is a disruption in the learning process, memory consolidation, and cognitive functions associated with disruption in LTP induction as a result of stress exposure (35, 36). It was shown that maternal deprivation from birth to 21 days of age for 3 hours daily leads to impaired spatial learning and memory in male Wistar rats at 60–80 days of age (37). In a previous study, we found that exposure to noise-induced stress for 2 or 4 hours during the third week of pregnancy, in addition to increasing basal corticosterone secretion in male offspring and impairing spatial learning and memory consolidation in these offspring, had a negative effect on the basal synaptic response recorded from hippocampal CA1 neurons and reduced LTP induction in rat offspring (38).

The precise mechanism by which lactational stress influences synaptic plasticity is not yet understood. Structural changes in the hippocampus during infancy appear to be associated with adult synaptic dysfunction, and the fact that high levels of stress-induced corticosterone have long-lasting effects on the offspring has been well established. Extensive studies support the view that both plasticity and pathological outcomes in adulthood may depend on circulating corticosterone levels, and these effects follow a U-shaped profile (28).

Exposure of lactating rats to noise-induced stress can impair spatial learning and memory, as well as synaptic plasticity of hippocampal CA1 neurons in adulthood by increasing the serum corticosterone levels of the offspring.

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