Original Article

Impaired Learning Due to Noise Stress During Pregnancy in Rats Offspring

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ABSTRACT

Background: Environmental noise is a known stressful factor,that induces alterations of various physiological responses in the exposed individuals. Extensive evidences from animal and human studies have indicated that stress influences cognitive functions. Studies have shown that chronic exposure to noise during pregnancy impairs neurobehavioral and reproductive functions and also reduces the body weight of the offspring. It seems that prenatal noise stress during last three months of fetal life damages the neurons in special areas of brain involved in cognition and impairs the activity of hypothalamus-pituitary-adrenal (HPA) axis. It is known very little about the effect of prenatal noise stress on learning. The aim of present work was to determine the effect of prenatal chronic intermittent noise stress on learning in rats.

Methods: Fifteen Wistar pregnant rats were exposed chronically to intermittent white noise (90-120dB, 350Hz) during the last two weeks of their pregnancy periods (dark cycle, 07:00Pm-07:00Am). Stressed and nonstressed puppies bred under normal condition up to 3 months of age. Both stressed and nonstressed adult male and female rats were trained in an equal 3 arms Y-maze with 20-25 Volts D.C. electrical footshock and a 12 Watts light stimuli as an active avoidance learning. Animals were trained one session daily and criterion condition response (CCR) was 90 percent of last session of training.

Results: Data showed that chronic exposure to noise during pregnancy impairs learning of stressed male rats significantly at all sessions ($P<0.01$). However, in the stressed female rats the response was decreased significantly only at the first two sessions ($P<0.05$).

Conclusion: The results indicate that prenatal noise stress may damage the neurons in special areas of brain such as hippocampus and alters cognition and behavioral functions.

Key words: noise stress, pregnancy, learning, rat.

Environmental noise is a known stressful condition, that induces alterations of various physiological responses in the exposed individuals [1] . Extensive evidences from animal and human studies have indicates that stress influences cognitive function[2]. The extent of noise disturbance depends on intensity, frequency, individual sensitivity, age, and sex [3,4]. Noise not only affects the nervous system of man, but also causes some psychological and psychosomatic problems[5,6] .Noise stress is one of the important environmental factors which affect pregnant mammals and their fetus. Noisy environments causes decrease in newborn body weight, stillbirths, fetal tratogenesis, and abortion[7,8]. Exposure to noise during pregnancy may affect the postnatal brain development and also may impair cognitive function[9]. Other studies suggest that postnatal exposure to noise impairs the retrival and short-term memory[10,11]. The extent of biological effects of noise depends on daily hours and season of exposure, so that in the afternoon, the noise is more effective[12]. On the other hand, studies have shown that sex hormones secretion is changed in stressor environment and have secondary effect on behavior such as cognition[13,14,15]. Stress changes neurotransmitter systems such as dopamine, norepinephrine, serotonine and also increases the beta-endorphine and hypothalamic met-enkephalin in rats[16]. Prenatally stressed rats have significantly higher level of corticotropin releasing factor (CRF) in the amygdala and show a greater release of this peptide in response to stimulation. Prenatal stress also results in a loss of left-side cerebral

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dominance, as indicated by the reduction in dopamine turnover in the prefrontal cortex[17]. Investigators have demonstrated that aging, stress, and glucocorticoids cause a variety of biochemical and morphological changes in the hippocampus which impair cognitive function[18]. The number of hippocampal neurons was markedly reduced in old compared to young rats[19,20], and the culprit was not simply the age, but the chronic effects of adrenal glucocorticoids which are secreted in the bloodstream in response to stress[21]. Stress also damaged hippocampal CA3 and CA4 neurons, but interestingly this damage was attenuated by testosterone, suggesting that age related decline in gonadal function may increase the hippocampal vulnerability to stress[22]. Morphological and electrophysiological changes in the hippocampus have functional consequences. For example, stress, like aging, impairs memory tasks dependent on hippocampal function[23]. However, it is known very little about the effect of prenatal noise stress on learning and the mechanisms underlying this effect are not clear. The aim of the present work was to determine the long term effect of prenatal chronic intermittent noise stress on active avoidance learning in rats.

Materials and Methods

Animals

Twenty-one (fifteen females and six males) Wistar adult young rats (3months aged) with weight range of 200-250gr (from Razi Institute, Hesarak, Karaj, Iran) were used. Animals were placed in inhalation units at ambient temperatures of 21-23 ^{o}C and a relative humidity of 45-65 percents. Tap water and food were available and lib. Animals were given two weeks to habituate to a reverse 12h light/12h dark cycle and settled in polycarbonate cages. The five females were time mated by placing them with two sexually active males in one cage unit until the occurrence of visible vaginal plaque during successive next three days as fertilization. All females were returned to their home cages after mating. Day of conception was designated as gestational day zero (GD-O). Pregnant rats were randomly assigned to either a gestational stress (GS) condition or a gestational non-stressed (GNS) condition.

Stress Procedure

A group of pregnant rats were exposed to white noise (90-120 dB, 350Hz). Exposure was started in the morning of GD-7 for the period of their last 2 weeks of gestation, from 07Pm to 07Am intermittently (6 sound-hours per day). Each sound - hour consisted of a programmed variable intensity (intermittent noise) from low to high dB every 2-3 minutes by a noise generator device. The noise generator was off automatically after one hour and then restarted one hour later. The noise exposure was discontinued just after childbirth. All control and exposed puppies bred under normal environment for 3 months.

Training Procedure

Adult control and stressed rats offspring were trained in a equal 3-arms Y-maze with using an A/D converter, a special software on a PC as active avoidance learning. Training was done as one session, 30 trails daily. Animals were conditioned, using a 12 watts light as conditioned stimulus (CS) and 20-25 volts electrical foot shock as unconditioned stimulus (UCS). Inter-trials interval (ITI) and inter-stimuli interval (ISI) were 60 and 5 seconds, respectively. Trained animals left the dark arms and enter in light arm during 5 seconds delay time (ISI). This effort was counted as conditioned response. Criterion condition response (CCR) was 90 percents in last session of training. Training sessions number was same for control (non-stressed) and stressed rats.

Statistical Analysis

The data, presented as mean± SE, were analyzed for significant differences by one way ANOVA, and t-test and levels of significance are indicated by asterisks: *P<0.01,**P<0.05,+P<0.02.

Results

Data analysis of learning in control group shows that the male rats (n=6) had thriving responses after 5.33±0.47 successive daily learning sessions in Y-maze, as we expected (90.56±1.24 percent or 27.2±0.4 proper responses). Proportion of the females (n=8) was 90%after 5±0.5 learning sessions (27 proper responses). There was not any significant statistical different between males and females of control group (fig.1).

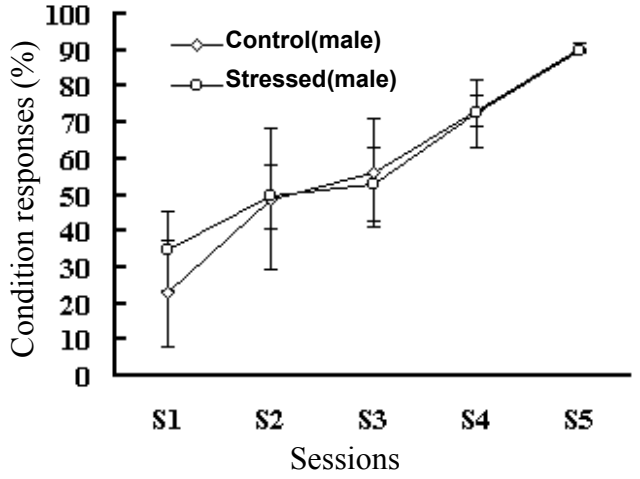

Figure1. Comparison between the percents of condition responses (%CRs) in control male and female rats offspring.

Our study shows that the level of learning in prenatal stressed rats was very low after 5 daily learning sessions. The disparity was more striking among the male rats; they had only 36.67 percent of correct responses (11±9.15 proper responses of 30 learning trials). The learning progression of prenatal stressed male rats was 79.56% less than control group (P<0.01,fig.2).

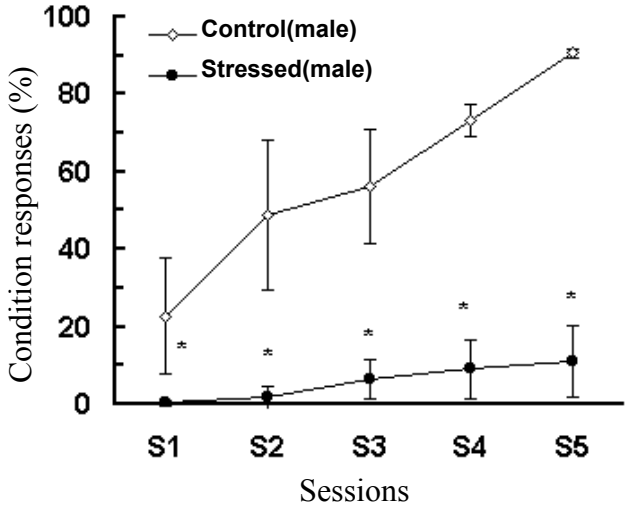

Figure 2. Comparison between percents of condition responses (%CRs) in control and stressed male rats offspring (* P<0.01).

Even after 7 sessions, they had only 77% thriving responses (20.7±8.34 of 30 learning trials). The learning progression of stressed female rats (n=9) was less than control group females after 5 successive daily learning sessions. In fifth session the females responed 76.67±16.48 percent properly (20.7 ±8.34 responses of 30 learning trials). This means that the stressed female rats had 13.33% less learning progression than control females. The differentiation was significant only during first and second sessions (P<0.05), not in sessions 3 to 5 (fig.3).

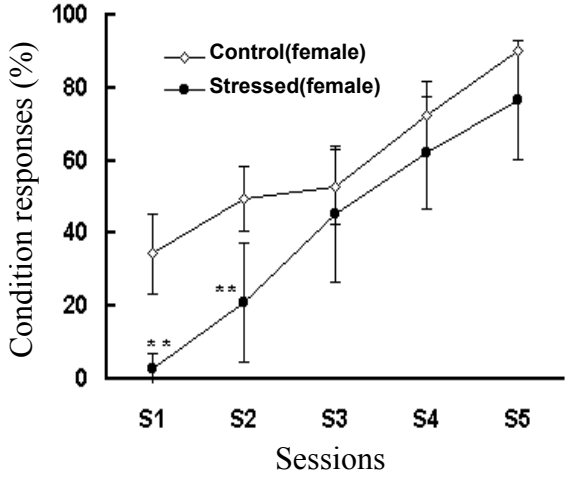

Figure 3. Comparison between percents of condition responses (%CRs) of control and stressed female rats (** P<0.05).

In fact, only two cases of stressed female rats could achieve to criterion responses of learning while others could not even after 8 learning sessions. Also the learning progression was compared in stressed male and female rats after consecutive 5 sessions training. The results show that the females performed significantly more proper responses than males (P<0.02, fig.4).

Discussion

Environmental intermittent loud noise during pregnancy had a significant impair on both male and female offspring's, prospective cognition behaviour. When the mothers had lived in a noisy environment during this period of life, then their offspring displayed significantly learning impairment compared to rats whose mothers had lived in a noiselessly condition. This effect is more sever in prenatal

stressed male offspring. Some investigations have shown that testostrone titers reduce in newborn and adult prenatally stressed males[30], and also secretion of glucocorticoides and androgens would increase in zona reticularis via activating the HPA[2,8-11].

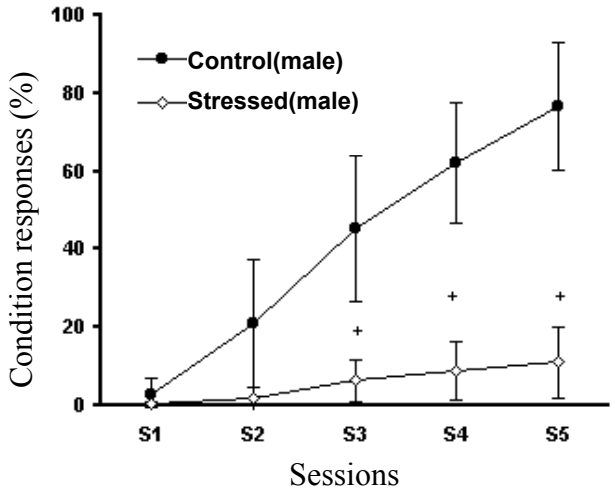

Figure 4. Comparison between percents of condition responses (%CRs) in stressed male and female rats offspring (* P<0.02).

The number of glucocorticoide receptors on soma of neurons responding to such hormones will decrease (down-regulation) in stressed offspring[9]. Other studies show that the mRNA of brain-derived neurotrophic factor (BDNF) in hippocampus decreases in stressed rats, and thereby hippocampal injury impairs the spatial learning[2,3]. However, hippocampal CA_3 and CA_4 neurons will damage by noise stress, but it can be prevented by testosterone administration[6]. Apical dendrites of hippocampal CA_3 neurons receiving mossy fiber input from dentate granule neurons will injure by stress[27]. Therefore, it can be suggested that both testes size and testosterone secretion will decrease in stressed males. Thus, decreasing testosterone secretion by noise stress during fetal life may damage the hippocampal neurons resulting impaired learning in stressed male offspring.

As it was mentioned, the effect of noise stress during fetal life on spatial learning of females was not significant. It seems that other factors may have compensatory roles against negative effects of noise on their spatial learning. As some studies have suggested that the noise stress during fetal life increases the ovaries weight while the weights of uterus and the brain medial pre-optic area will be decreased. Thereby secretion of gonadotrophines and estrogen will be increased just after birth, and estrogen can change brain activity, and plasticity of neural circuits and thus improve the learning[5,20]. In spite of decreasing the lutein hormone releasing (LHRH), LH, FSH, and prolactin hormones, the estrogen can play as a compensatory factor Thus, it seems, there is a possibility that in stressed female rat offspring, estrogen can compensate a part of negative effect of noise during fetal life on learning when compared with stressed male offspring. These results suggest that high intensity and low frequency noise during fetal life may change physical growth parameters, neuronal plasticity, hormones, and neurotransmitter systems in brain resulting in reduction of brain ability for acquisition.

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