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Maternal exercise decreases maternal deprivation induced anxiety of pups and correlates to increased prefrontal cortex BDNF and VEGF

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ABSTRACT

Maternal deprivation (MD) may cause neuropsychiatric disorders such as anxiety disorder by negatively affecting the cognitive functions and behavior in pups. The aim of this study is to investigate whether maternal exercise during pregnancy has beneficial effects on anxiety that increases with MD, and on the levels of VEGF and BDNF which have anxiolytic effects on the prefrontal cortex, the anxiety-related region of the brain. The anxiety level in the deprivation group was greater than the control group and found more in male than female pups. The prefrontal cortex VEGF and BDNF levels were decreased in the deprivation group compared to control group while serum corticosterone levels were increased in the deprivation group. Anxiety and serum corticosterone levels were decreased in maternally exercised female and male pups, while the prefrontal cortex VEGF and BDNF levels were increased, compared to sedentary mother's pups. These results indicate that maternal exercise may attenuate the negative effect of stresses such as maternal deprivation that can be encountered early in life.
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In mammals, normal development and growth is significant for mother–pup relation; maternal deprivation (MD) is a major stress which may cause physiological and behavioral changes during brain development. Internal and external factors can affect the brain development [24]. Stressful situations in early development period, such as MD, may cause neuropsychiatric diseases which affect the later periods of life, such as anxiety disorder [17].

MD is a stress model that is widely used in rodents in their early life periods [29–32]. In later periods of life, permanent changes may occur in the endocrine systems of the maternally deprived animals [31,32,34]. MD may cause anxiety-like behavior by causing structural changes in the prefrontal cortex (PFC) [21]. Also, the hypothalamic levels of the neurotrophic factors such as brain derived neurotrophic factor (BDNF), with known anxiolytic effects, change during maternal deprivation, and this change alters the cell proliferation and maturation differentially in females and males [34].

Approximately on postnatal day 4, the infant rat enters the so-called stress-hyporesponsive period (SHRP) [24]. This period lasts until postnatal day 14 and is characterized by reduction of adrenal sensitivity. It appears that low levels of corticosterone during SHRP are essential for a normal development, because exposure to high levels of corticosterone has widespread deleterious effects on the developing brain [24]. In our previous studies, we showed that the infant brain protected from MD in SHRP. Thus, in this study MD was applied after SHRP (postnatal days 18) [29,30].

It has been showed that males and females were affected differentially from MD. Prolonged MD increased the glucocorticoid receptor expression in male rat brains [26]. When maternally deprived males become adults, they feel much anxiety and fear than females [26,34]. We have previously reported that the SOD enzyme activity increases in the striatum and like GPx enzyme activity and TBARS levels in the PFC in maternally deprived males. No change is observed in maternally deprived females [31].

It is known that regular exercise ameliorates the neural structures and functions. We have been demonstrated that exercise enhanced the cognitive functions [33]. It was also showed that exercise increased the neurotrophic factors such as BDNF and angiotrophic factors such as Vascular Endothelial Growth Factor (VEGF) in hippocampus and blood [25].

Recent research is directed towards emending the negative interaction in pups due to MD by the positive effects of exercise. In studies on this topic, it was found that both the forced exercise and the voluntary exercise ameliorated behavior and learning negatively affected by MD [10,13]. However, the effects of the maternal

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exercise during pregnancy on pup's anxiety caused by MD and interrelated on the PFC are not known.

The aim of this study is to investigate the effects of maternal regular aerobic exercise on the anxiety levels of the pups in preadolescent period, and on the prefrontal cortex BDNF and VEGF levels.

Eight-week-old male and female Wistar Albino rats were purchased from Experimental Animal Laboratory. The pregnancies of the groups were controlled by estrous monitoring. The female rats ($n = 8$) were equally divided into sedentary and exercised groups. The day of birth was designated as postnatal day 0. Pups were divided into two groups: maternally exercised, sedentary. Each group consists of two sub-groups: maternally deprived, control. Each group consists of female and male rats ($n = 8$). The animals were maintained under standard colony conditions with a 12 h light/dark cycle (lights on 07:00 h), at constant room temperature ($22 \pm 1\,^{\circ}C$), and humidity (60%). Food and water were available ad lib. All 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 Eylul University School of Medicine.

Exercised mothers were trained to the treadmill before pregnancy at 5 m/min for 10 min/day, 5 days. After breeding with estrous monitoring, the mothers started to exercise at 8 m/min for 30 min/day, 5 days/week. In the last week of pregnancy, the pace of the exercise was reduced to 6 m/min and the exercise had continued until birth [10].

MD took place on PND 18 as previously described [29,30]. In brief, mothers from the deprived groups were removed in the morning (beginning at 09:00 h) and pups remained in their home cages for 24 h. On PND 19 the mothers were returned to pups. During separation, the pups of each litter were kept together and warmed by a heating pad ($33 \pm 0.2\,^{\circ}C$) and they were provided access to food and water.

The remaining rats were weaned on day 22 and when the pups were 24 days old, their anxiety levels were evaluated using the open field and elevated plus maze tests. The recording and analysis of the anxiety levels were performed with the HVS image video tracking system.

Locomotor activity was measured with an open-field test; 1 m × 1 m and 50 cm in height, video camera installed 2.5 m above apparatus. Each rat was placed in the center of the open-field and then locomotor activity (ambulation) was measured for 5 min in a sound-proof observation room illuminated with controlled light (100 lx).

The animals were tested for anxiety behavior in the elevated plus maze. This consisted of a central platform (5 cm × 5 cm) with two open arms (50 cm long, 10 cm wide and 0.5 cm high borders) and two closed arms (same dimensions as the open arms only with 40 cm high walls) that were elevated 50 cm above the ground. Rats were placed on the platform facing the open arm and were observed for 5 min. The total number of entries into the open and closed arms as well as the time spent in the open and closed arms was measured.

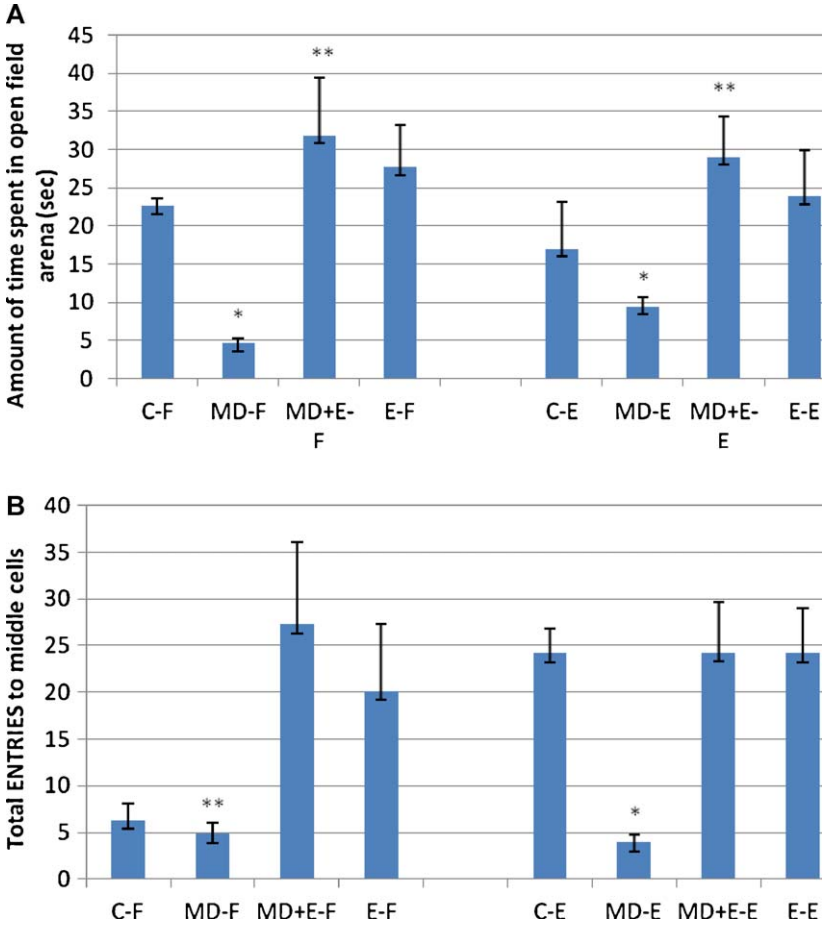

Fig. 1. Open field test results; (A) Percentage of the time they are moving the open field arena, (B) Number of entries in the open field arena in the middle cells. $^{*}p < 0.05$ compared with the same sex of control group; $^{**}p < 0.05$ compared with the MD+E-F group (C-F: Control females, MD-F: deprived females, MD+E-F: maternally exercised deprived females, E-F: Maternally exercised females, C-E: Control males, MD-F: deprived males, MD+E-F: maternally exercised deprived males, E-F: Maternally exercised males).

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