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IMMUNE-BEHAVIORAL CHANGES AFTER PREGESTATIONAL PSYCHOLOGICAL STRESS

PROJESTASYONEL PSİKOLOJİK STRES SONRASI BAĞIŞIKLIĞA DAYALI DAVRANIŞSAL DEĞİŞİKLİKLER

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Abstract

Gestational stress has been extensively studied in order to clarify its effects on behavioral and neurodevelopmental in both mother and offspring. Our study was deflected to investigate the pregestational psychological stress, the relationship between parameters of the immune system and the neurobehavioral changes (spatial memory).

The stress was applied in female albino wistar rats, were submitted to chronic restraint stress for 1h/day for 4 days a week during 5 weeks before gestation. The behavior of rats and offspring was assessed in the Morris water maze test and the immune system by measuring the plasma concentration of IgG, which are the only immunoglobulin able to cross the placenta. Our results showed a change in the concentration of IgG, immune system cells and disturbance of spatial memory (Morris water maze).

Keywords: pregestational stress, immune parameters, spatial memory.

Özet

Jestasyonel stres, hem annedeki hem de anne karnındaki bebekteki davranışsal ve nörogelişimsel etkileri açıklamak için kapsamlı bir şekilde çalışılmaktadır. Bu çalışma, projestasyonel psikolojik stres ve bağışıklık sistemi parametreleri ve nörodavranışsal değişimler(uzamsal hafıza) arasındaki ilişkiyi incelemek için oluşturulmuştur.

Stres, hamilikten önce 5 hafta boyunca haftada 4 gün birer saat olmak üzere kronik kısıtlayıcı strese maruz bırakılan dişi albino wistar sıçanlarında denenmiştir. Sıçanların ve yavruların davranışları, Morris su labirenti testiyle ve plasentayı geçebilen tek immunoglobulin olan IgGnin plazma konsantrasyonunu ölçen bağışıklık sistemiyle değerlendirilmiştir. Çalışmamızın sonuçları IgG'nin konsantrasyonunda, bağışıklık sistemi hücrelerinde ve uzamsal hafıza bozulmasında(Morris su labirenti) bir değişiklik göstermiştir.

Anahtar Kelimeler: *Projestasyonel stres, bağışıklık parametreleri, uzamsal hafıza.*

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1. Introduction

Stress is an inevitable experience in life that can disrupt cognitive processes, neuroplasticity, endocrine and immune system in animals and humans (Dantzer and Mormede, 1995).

Chronic restraint stress models are the most popular for studying the mechanisms of impairments or cognitive disturbances (Chen et al., 2010; Yi et al.,2013). Glucocorticoids are able to modulate many cellular processes such as energy and neurotransmitter metabolism (Datson et al., 2008) which are all the intervening elements in response to stress in the restoration of homeostasis. Authors have shown that the mother of both human and animals exposed to environmental factors such as emotional stress (Dudley et al., 2011; Yong et al., 2012; Neigh et al. , 2013) can influence the behavior and development of the offspring (Mychasiuk et al., 2011; Inhasz Kiss et al., 2012; Huang et al., 2013). These changes may be mediated by intrauterine exposure to glucocorticoids secreted during activation of the HPA axis of the mother by stress. These can pass through the placenta, thereby enriching the fetal brain development (charil et al., 2010).

Other studies have shown a relationship between maternal anxiety in late pregnancy and the emotional and behavioral difficulties, persisting after six years, and are observed in both boys and girls during four years. This leads us to think about the quality of the mother - child relationship that plays an important role in the harmonious development and the subsequent balance of that individual. Disturbances of this relationship can lead to such serious emotional disorders.

To evaluate the concept of stress, we should see the life events that have long occupied a central place and that would likely be a source of stress. These correspond to significant events that occur in the life of the subjects stressing, the assumption that the stress resulting from the accumulation of changes that require an adaptation (Graignic-Philippe et al., 2005).

In order to clarify the effects of chronic restraint stress in rats applied before mating, we proceeded to study the immune system and trying to find relationships that may exist with the endocrine and nervous system and the neurodevelopment of the offspring. This was facilitated by the establishment of animal models of behavioral disorders such as the Morris water maze What could contribute to a better understanding of the physiological mechanisms and neurobiological disturbances.

2. Methods

2.1. Animals

Albino Rats coming from Pasteur Institute of Algiers were used during this study.

The animals were housed in specific cages maintained in natural photoperiod temperature with standard conditions: an average temperature of 22 ± 4 º C and a relative humidity of 50-70%. After a three weeks of adaptation , we selected 34 females according to the weight with an average weight of (140-170) grams then we divided them into 2 experimental batches: each batch of 17 rats.

2.2. Induction of Stress

The model of restraint stress in this study according the method of Bardin et al. in (2009). It involves placing the rats in a cylindrical bottle perforated plastic one hour in the morning at the same time for 4 days a week, for 5 weeks in the same animal room. When the restraint stress procedure was finished (24 h after the last day), all female rats were housed in pairs with a male for 6 days for mating, after-parturition, 15 male and 15 female were randomly selected pups from each batch to study the effects of this type of stress on mothers and neurodevelopment of the offspring. The experimental procedures were carried out according the National Institutes of Health (USA) and the Declaration of Helsinki.

2.3. IgG Analyses (Whicher et al., 1983)

The blood collection is done starting from the lacrimal vein at the end of the application of chronic restraint stress. The blood samples are collected in the heparinized tubes then centrifuged at 5000 rpm for 05 minutes. The IgG assay was performed by the immunoturbidimetric method. The latter is based on determining the endpoint IgG concentration by photometric measurement of an antigen- antibody reaction between anti- IgG antibodies present in the sample. The measurement is done using an OLYMPUS player on a wavelength 570 nm, and it equipped with computer software that automatically calculates the calibration range and gives us direct value to the desired unit.

2.4. Behavioral Tests

2.4.1. Morris Water Maze

Apparatus

The Morris Water Maze is used to identify and assess spatial learning and memory in rodents (Morris, 1981). Morris tank is a circular pool of 120 cm diameter and 60 cm depth, made of polypropylene and installed on a support. It is divided into four quadrants; one of the latter comprises a slightly submerged platform; 1 cm below the water surface (the target quadrant). Extra- maze cues were geometric located around the pool to provide a spatial configuration of the task. It is filled with water to 30 cm deep. The water temperature is maintained between 22 and 32 °C.

Maternal Study

The Morris test includes four days of trial with five passages per day (3 days with platform (learning) and the 4th day 2 passages with platform and 3 without platform (memorizing). The rat is placed in the water to the periphery different places, she swims to find the platform and then it is removed from the water. The test is redone with only a 60 second pass. If the rat is not the

platform after 60 seconds the transition is complete and the experimenter places the animal on the platform for ten seconds. The platform is removed on the 4th day of the test and the test lasts 60 seconds. All tests are filmed and the three parameters register are: the time spent in the target quadrant and the number of entries in the same quadrant.

Offspring Study (Adolescence age in postnatal days 50 and 51)

The test was according to the method of Morris in 1981. Offspring were subjected to the test for two consecutive days. The first test session (Day 50) includes five trials with a platform for the acquisition and familiarization tours where the animal learns to locate the location of the platform and take refuge there. The second test session (Day 51) includes two tests without the platform for retention. The parameters measured are: the time needed to find the submerged platform in the quadrant designated as target (latency) and the time spent in the same quadrant.

3.Data Analysis

All results were expressed as Mean ± Standard Deviation (M ± SD) and analyzed using Student's t-test with the Minitab program (version13) comparing between the different groups. The significance level of P ≤ 0.05 was considered.

• Differences are considered statistically significant at $p < 0.05$.

4. Results

4.1. Plasma IgG Concentration (g/l)

Statistical analysis of these results showed a highly significant increase in IgG of stressed rats (** 4.36 ± 0.06 g/l) compared with control rats (3.35 ± 0.12 g/l). Figure 1.

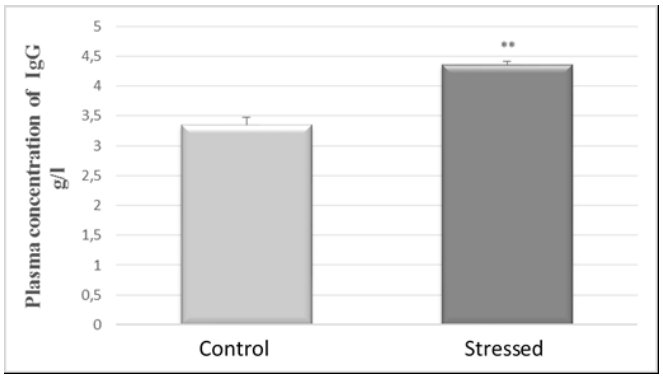

Figure 1: Changes in plasma concentration of IgG (ng / ml). (m ± s; Ns: non-significant difference p > 0.05; *p <0.05; **p < 0.01; ***p < 0.001)

4.2. Immune System Cells

Immune cells are divided into innate immunity cells (GB, MONO, PLQ) that are able to capture, present the antigen and destroy foreign elements and adaptive immunity cells (LYMPH). Figure 2 .

The results show a decrease in the rate of white blood cells (8.22 ± 0.60 µl) and monocytes (0.57 ± 0.12 µl) of stressed rats relative to white blood cell rate (9.56 ± 1.28 µl) and monocytes (0.86 ± 0.10 µl) in control rats. However, we did not find differences in the rate of lymphocytes (5.63 ± 0.77 µl) and platelets (705.33 ± 138.16 µl) of stressed rats compared to lymphocyte ratio (5.89 ± 0.84 µl) and platelet (599 ± 124.30 µl) in control rats.

Statistical analysis showed a significant decrease in the rate of white blood cells and monocytes in stressed rats compared to control rats (p * <0.05). However, the rates of lymphocytes and platelets showed no significant difference in the stressed rats compared with the control rats (p > 0.05). Figure 2.

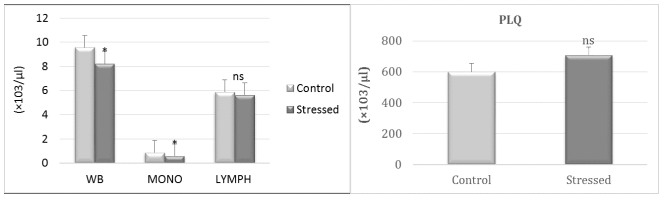

Figure 2: Cells of the innate and adaptive immune system in control and stressed rats. (m ± s, n = 17 control, n = 17 stressed). (Ns: non- significant difference p > 0.05; *p <0.05; **p < 0.01; ***p < 0.001).

4.3. Morris Water Maze of Mothers

The results in figure 3 show a significant decrease in the number of entries figure 03(A) (D3 : 12.64 ± 4.33 s *; D4 : 8.72 s ± 3.98 s*), and the time spent in the target quadrant figure 03(B) (D 3 : 20.5 * ± 2.08 s; D 4 : 14.5 * s ± 3.11) in the third (learning) and fourth (memorizing) days in stressed rats compared to the number of entries (D3 : 21.3 ± 4.52 s; D 4 : 16.30 ± 4.38 s) and the time spent in the target quadrant (D3 : 25.75 ± 1.71 s; D 4 : 25.25 ± 5.56 s) in control rats.

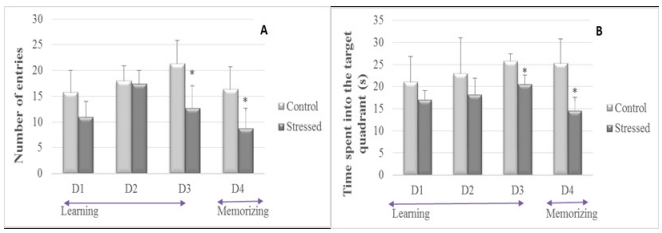

Figure 3: Morris water maze test parameters in control and stressed rats. (A) The number of entries in the target quadrant. (B) The time spent in the target quadrant. (m ± s, n = 17 control, n = 17 stressed). (Ns: non- significant difference p > 0.05; *p <0.05; **p < 0.01; ***p < 0.001).

4.4. Morris water maze of offspring

Adolescence Age (postnatal days 50 and 51)

Within two days of the Morris water maze test, we have seen remarkable difference in latency to find the submerged platform and the time spent in the target

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quadrant but insignificant between groups coming from control and stressed mothers in 51 days. Figure 4.

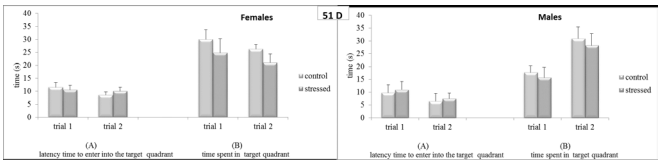

Figure 4: Latency time in the target quadrant in PND 51 (A). Time spent in the same quadrant (B) of males and females offspring. (m ± s , n of the offspring from control mothers (15 males, 15 females) and stressed mothers (15 males, 15 females).(Ns : non-significant difference p <0.05; *p <0.05; **p < 0.01; ***p < 0.001)

5. Discussion

In this study, the significant increase in latency time with decrease of the time spent in the target quadrant in the Morris water maze of rats subjected to chronic restraint stress. Which is explained by the disruption and weakening of learning and memory abilities (Xu et al., 2009). Because the main physiological responses of chronic stress include activation of the hypothalamic-pituitary - adrenal (HPA) axis and the medulla Sympatico-system , by which the levels of corticosterone and catecholamines may be modified (Cohen and Hamrick, 2003; Yi et al., 2013),induced a change in cognitive functions including learning and spatial memory. These are linked with specific alterations of the hippocampus which depend largely on these behavioral tasks (Yi et al., 2013; Vann and Albasser, 2011).

In stressful situations, the hypothalamus receives direct stimulation of the limbic system and noradrenergic stimulation from the locus coeruleus and nucleus of the solitary tract (Carrasco and Van De Kar, 2003; Itoi, 2008). In response to these stimuli hypothalamus releases CRH activates the adenohypophysis in turn secrete ACTH. It induces the synthesis of glucocorticoids by the adrenal glands. These hormones are involved in the stress in many functional regulations in the metabolism and the central nervous system (Morilak, 2005). So there is evidence that emotional stress can affect many integrator circuits between the immune, nervous and endocrine system in animals and humans (Dantzer and Mormede, 1995). As shown in our study, when we explored the immune system by studying immunoglobulin (IgG).These molecules are the first that would be released into the blood stream and they are the most abundant of the five classes of immunoglobulins. They are the only ones that are able to pass from mother to child during pregnancy through the placenta . In several studies, these molecules have demonstrated neuroprotective effects (Hulse et al., 2008; Zhang et al., 2012). The human immunoglobulin (IgG) is the main component of the protection against lesions of dopaminergic neurons from 6 - hydroxydopamine (6- OHDA) (Zhang et al., 2012). IgG has traditionally been thought to be produced by mature B cells only , but recently has been shown to be produced by neuronal cells. Huang et al en (2008) showed that IgG can be produced by the central neurons in rats and has previously been shown that IgG are abundantly produced by neurons in the cerebral cortex , hippocampus, dentate gyrus , cerebellum, the pons, the medulla and spinal cord , it is synthesized by the same intraocular eye cells in human (Niu et al., 2011). Although the function of the neurons immunoglobulins IgG is poorly understood, it has been suggested that IgG neurons are involved in maintaining the stability of the nervous system. These molecules become toxic to dopaminergic neurons when released in large quantities. Oxidative stress due to changes in the concentration of IgG under the influence of physiological glucose concentrations (Newkirk et al., 2003).

The decrease in white blood cells after restraint stress may be caused by their redistribution in peripheral tissues, such as skin and lymph nodes, where the destruction of the stem cells and exerted immunosuppression by glucocorticoids and even by catecholamines (anti activity -inflammatory and immunomodulatory). By inhibiting T cell proliferation, decrease the bactericidal activity of macrophages and suppress the cytotoxic activity of natural killer (NK) cells. However, glucocorticoids may also exert immunostimulatory properties of B cells play sometimes a role of immunostimulant and sometimes immunosuppressive (Steele, 2002). Leukocytes possess receptors for adrenaline, sex steroids, insulin, prolactin, growth hormone and thyroxine. Monocytes from bone marrow have not been only a phagocytic activity but also secrete enzymes , proteins , prostaglandins , cytokines and even ROS (reactive oxygen species) and NO (reactive nitrogen species) (Pereira et al., 1996). Which are important in the defense against pathogens and tumor cells. (Hibbs et al., 1988; Macmicking et al., 1997). High levels of cortisol stimulate apoptosis of thymocytes and can cause lymphopenia and monocytopenia (Nascimento et al., 2004).

The immune system in turn also incorporates neural information. Because primary and secondary lymphoid organs are innervated by sympathetic and cholinergic nerve endings. Leukocytes have receptors for most neurotransmitters released by these nerve endings, which explains the impairment of the immune system and its relationship with the nervous and endocrine system (Besedovsky and Del Rey, 1996). The biochemistry of neuronal dysfunction was also demonstrated in the Morris water maze test in which we also found changes in capacity memorizing of the offspring but still meaningless. These were demonstrated by the number of entries in the target quadrant and the time spent in the same quadrant (Leslie et al., 2000; Takuma et al., 2012). On the other hand, in our previous studies we have shown that this type of stress has contributed to the emergence and development of neurobehavioral disorders such as depression and anxiety in the mothers and their descendants (Haloui and Tahraoui, 2014). The hyper activation of the HPA axis of mothers activates the HPA axis of the offspring that affects the mother-child relationship and influencing the development of the embryonic brain and changing the behavior of the offspring permanently (Mychasiuk et al., 2011; Baibazarova et al.,2013; Haloui and Tahraoui, 2014; Baquedano et al., 2011).

5. Conclusion

The quality of relationships between a –mother-child plays an important role in the harmonious development and the subsequent balance of that individual. Disturbances of these relationships can lead to such serious emotional disorders. These are dependent on the timing and the type of stressor (Kapoor et al., 2009).

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