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Effects of Pregestational Chronic Restraint Stress on the Generation of Psychological and Neurobehavioural Disorders in Female Wistar Rats and their Offspring

Meriem Haloui[1], Abdelkrim Tahraoui[2]

[1, 2] Applied Neuroendocrinology Laboratory, Department of Biology,
Faculty of Science, University Badji Mokhtar Annaba, BP 12 23000, Annaba, Algeria
E-mail: mariehaloui@yahoo.fr.

Abstract: ***The present study aims to put some tracks values especially with regard to the likely transmission over generations of cognitive and behavioural damages. This by investigating the effects of chronic restraint stress (1hour /day, 4 days / week for 5 weeks) applied before gestation in mothers on the generation of anxiety and depression-like behaviours and their effects on the hypothalomo-pituitary-gonadotroph HPG axis by measuring the concentration of progesterone in rats after stress. After birth, the development of the offspring was studied. Our results show that chronic restraint stress involved a development of anxiety in the Elevated Plus maze test (EPM) (anxiety like behaviour), increased immobility during Forced swimming test (FST) (depression like behaviour). Disturbances of the HPG axis were revealed by the highly significant elevation of plasma progesterone concentration. The offspring male and female chowed*** **hyperactivity** ***disorder in the Open Field test (OF) at the age of adolescence.***

Keywords: Chronic Restraint Stress, Anxiety, Depression, HPG axis, Offspring, Neurobehavioural Disorders.

1. Introduction

Several studies have shown that emotional and environmental stressors can disrupt brain function, they are considered as a key factor in the genesis and the evolution of neuropsychiatric disorders **[1, 2]**. The use of restraint stress as a psychological stressor has been largely evoked **[1, 3]**, and interaction between environmental and genetic factors may participate in the installation of depression and disruption of homeostasis in humans **[4]**. The hypothalamic-pituitary -adrenal (HPA) axis is a key endocrine adaptor against stressors. It plays an important role in the pathophysiology of stress-related psychiatric diseases such as depression and anxiety disorders **[5].**

Some other behavioural changes can be considered as parallel symptoms of depression, such as decrease in sexual and aggressive behaviours **[6]**, disturbances of the oestrus cycle **[7]**. Some authors hypothesize that high anxiety is a risk factor of the development of other mood disorders **[8]**.Recent studies noted that the restraint stress induced an anxious and depressive behaviour in the rodents (Huynh et al., 2011; Shuichi al., 2012). Other studies did not find such changes after stress application **[3, 9, 10]**.

Some studies were demonstrated that reproductive functions are suppressed under various stress conditions like restraint, strenuous exercise, malnutrition, infection and surgical trauma **[11]**. Prolonged or chronic stress causes anovulation that result in infertility due to the suppression of gonadotrophic hormones **[12]**.

Environmental factors such emotional and stressful events **[13]** to which a mother is exposed during pregnancy in human and animals **[14]** can influence behavioural and social development of the offspring **[15]**. Prenatal glucocorticoids GCs exposure programs several central dysfunctions in offspring (Diaz et al., 1998). we aim by this study to examine anxiety related (elevated plus maze) and depression-like behaviours (forced swimming test) of rats during 5 weeks of stress in an attempt to find possible associations between HPA axis and these behaviours, HPG axis; progesterone, and the development of the offspring when stress is applied before gestation.

2. Methods

2.1. Animals

Rats albino coming from Pasteur Institute of Algiers were used during this study. The rats were acclimatized to the natural photoperiod standards' conditions: an average temperature of 22 ± 4 º C and a relative humidity of 50-70%. After a three weeks adaptation period, we selected 34 females according to the weight with an average of (140-170) grams then we divided them into 2 experimental batches: each batch of 17 rats. After parturition, we randomly selected 15 male and 15 female pups from each batch for the behavioural studies.

2.2 Induction of stress

Our model of stress is based on that of **[16]**, at the end of the pallet of stress; a behavioural evaluation was carried out.

2.3. Behavioural tests for maternal study.

2.3.1 Plus maze test (EPM)

The apparatus was based on the method of **[17].** The EPM was made of wood and consisted of two open arms and two

closed arms, crossing each other in the form of a plus. the two opposite open arms measured 50×10 cm (surrounded by a 1-cm-high plexiglas), and the two closed arms measured, 50×10×50 cm, with a central platform of 10×10cm area .the whole apparatus was situated at a height of 50 cm above the floor. The floor of the maze is made out of plexiglas, in order to avoid urine impregnation. At the beginning of each trial, animals were placed at the center of the maze, facing an open arm. All trials were conducted between 08-09h a.m. After each trial, the maze was cleaned with ethanol solution (10% v/v). The parameters measured for the behavioural evaluation are : Number of entries of the animal into the open and closed arms, and the time spent there.

2.3.2 Forced swimming test (FST)

The forced swim test is frequently used to examine depression-like behaviour. The method of **[18]** was applied. In the first day after the pallet of chronic restraint stress, animals were introduced individually into an aquarium filled with water at 22-23°c to a height of 35cm from the base, and forced to swim for 15minutes in the first session (day 1). On day two (second session of approximately 24 hours), all the animals were reintroduced into the same aquarium for 5 minutes and the session was filmed for the behaviour analysis. Times of immobility, swimming and climbing are calculated.

2.4 Behavioural test for offspring study

2.4.1 Open Field test (Spontaneous locomotor activity in postnatal day 45)

This test was used for evaluate the behaviour of the offspring in postnatal day 45. The test based on that of **[19]**, it measures the locomotor activity and habituation response of animals in a novel environment and the depression like behaviour. The apparatus is composed of a base surrounded by plexiglas parapets, whose measurements are respectively of 70cm×70cm×40cm. the floor is in the form of squares of 10cm×10cm of diameter, it was divided into two zones: central and peripheral zone each one is of 35cm. The animal is placed in the center of the device, its displacement makes it possible to measure the number of squares crossed (the distance) as well as the time spent in each zone and the sequence is filmed during 5minutes. This test indicates locomotor activity and anxiety behaviour respectively. The latter is more pronounced when the rat spends more time in the peripheral zone. As for the central area, exploration represents a sign of reduced anxiety. The measured parameters are; the time spent in the center of the device, time spent in the periphery, and it distance covered.

2.5. Serum progesterone assay

The taking away is done starting from the lachrymal vein at the end of the application of chronic restraint stress. The blood samples are collected in the heparinized tubes then centrifuged at 1500 rpm for 10 minutes. Plasma was used for progesterone assay. The progesterone is proportioned by the conventional ELISA method **[20]**. Measurement is done using a reader ELISA TECAN Magellan provided with data-processing software which calculates the range standard automatically and the value of the progesterone to the desired unit gives us directly.

3. Data analysis

The results are presented as mean ± standard error (SEM), and were analysed by using test T of Student with the program Minitab (version13). They are regarded as being significant $p < 0.05$.

4. Results

4.1. Plus Maze Test (EPM)

The elevated plus maze assesses the rats natural tendency to explore a novel environment. It is well accepted that anxiogenic factors lead to decreased exploration of the open arms of the EPM. When exposed to the plus maze test, stressed rats displayed a significant decrease of the total time spent into the open arms (9.4* ±1.52 s) when compared to the control rats (19.6 ±7.73 s) **(Fig.1. B).** Results showed also a very significant increase of the time spent into closed arms (357*** ±25.1 s) when compared with the control (292.6 ±7.8 s) **(Fig.1. D).** In order to measure overall motor activity in the elevated plus maze, the total number of arm entries was also examined. The number of entries to open and closed arms measures the overall locomotor activity. This measure checks whether differences in open arm exploration were due to changes in overall activity in the EPM. Our results showed that the number of entries into the open and closed arms respectively of stressed rats (1.2* ± 0.44 s ; 2** ± 1.22 s) present an overall reduction in exploratory behaviour when compared with unstressed rats (3.2 ± 1.3 s ; 5.4 ± 1.14 s) **(Fig.1. A, C).**

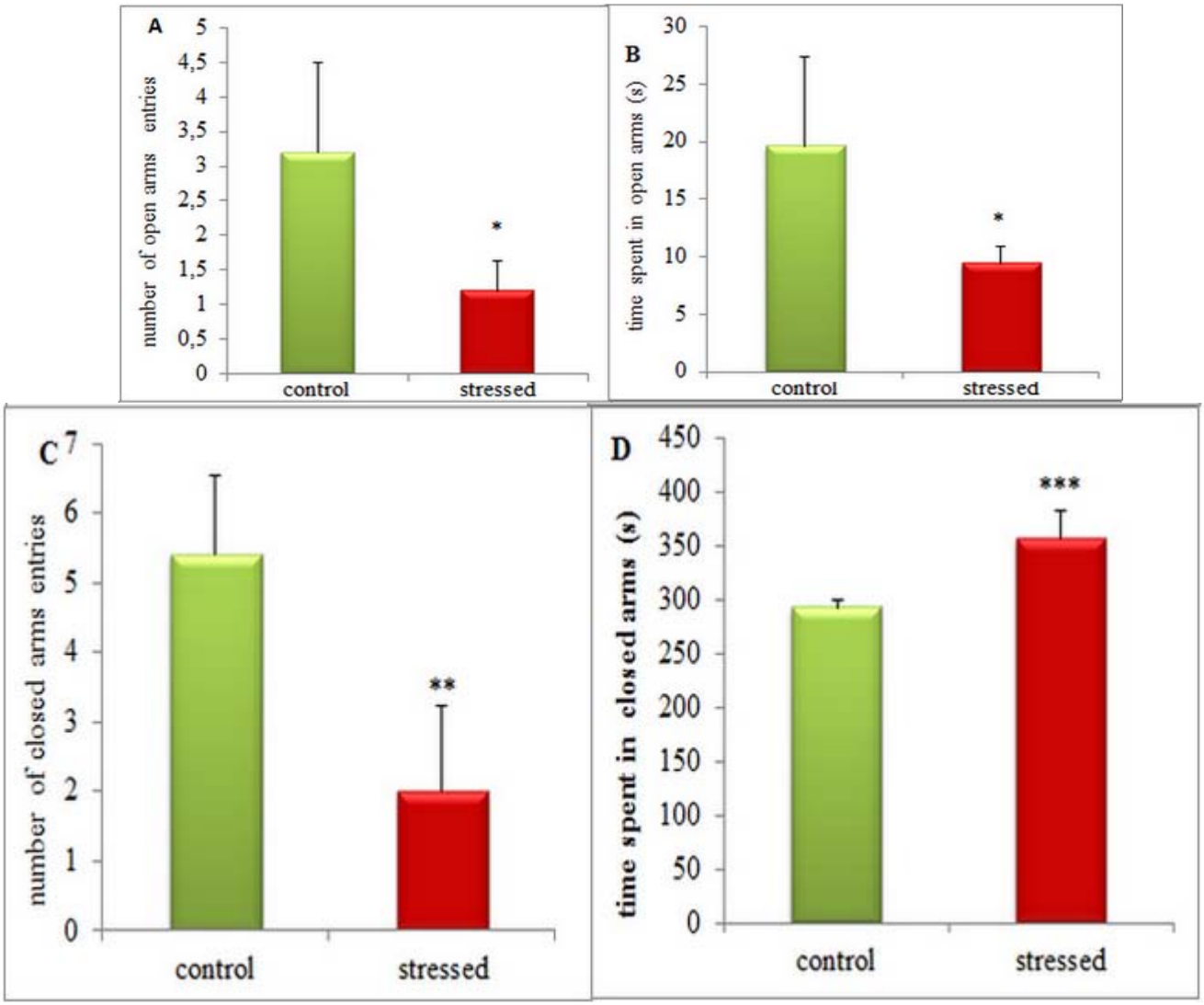

Figure 1: Effects of chronic restraint stress on behaviour of rats in the plus maze test .
(A ,C) Number of entries into open and closed arms respectively ,total time spent into open and closed arms (B ,D) respectively. (m ± SD; * p < 0.05; **p < 0.01; ***p < 0.001)

4.2. Forced Swimming Test (FST)

Stressed rats demonstrated a significant increase in immobility time (214.6* ± 21.8 s) when compared to the control rats (169.6 ± 33.7 s) **(Fig.2)**, but there is no significant decrease in both swimming (130.2 ± 24.4 s) and climbing (211.6 ± 15.8 s) time Compared with control rats in swimming (158.6 ± 23.4 s) and climbing (228.6 ± 16.3 s) behaviours.

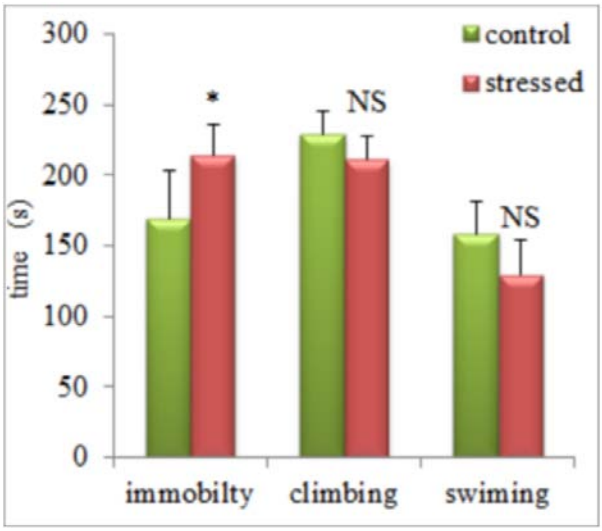

Figure 2: Effects of chronic restraint stress on behaviour of rats in the forced swimming test.
(m ± SD; * p < 0.05; **p < 0.01; ***p < 0.001).

4.3 Variation of plasma concentration of progesterone (ng/ml)

Variation of plasma concentration of progesterone in stressed rats present a highly significant increase (74, 83** ± 9, 16 ng/ml) compared to the control (46, 09 ± 7 ng/ml) **(Fig.3)**.

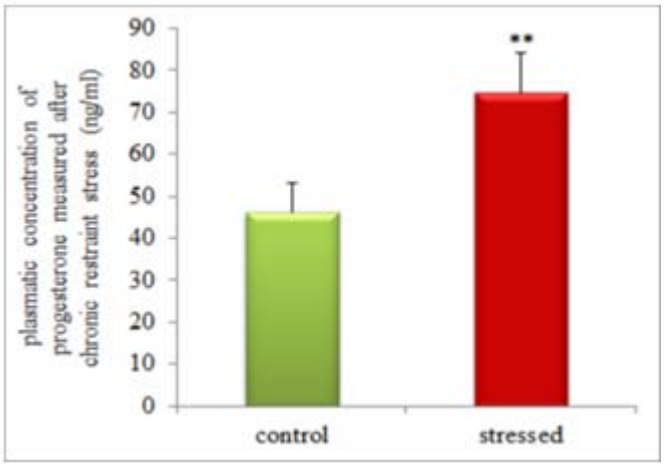

Figure 3: Variation of plasma concentration of progesterone (ng/ml).

(m ± SD; * p < 0.05; **p < 0.01; ***p < 0.001).

4.4 Open Field test (OF Spontaneous locomotor activity in postnatal day 45)

Offspring demonstrated a very significant increase of the distance travelled by females (1535 ± 51.7 cm) and males (1508.3 ± 82.9 cm) of stressed mothers compared to the control females (1196 ± 35.6 cm) and males (1186.7 ± 59.9 cm) respectively. However, there is no significant time spent in the central area of the apparatus compared to the control **(Fig.4)**.

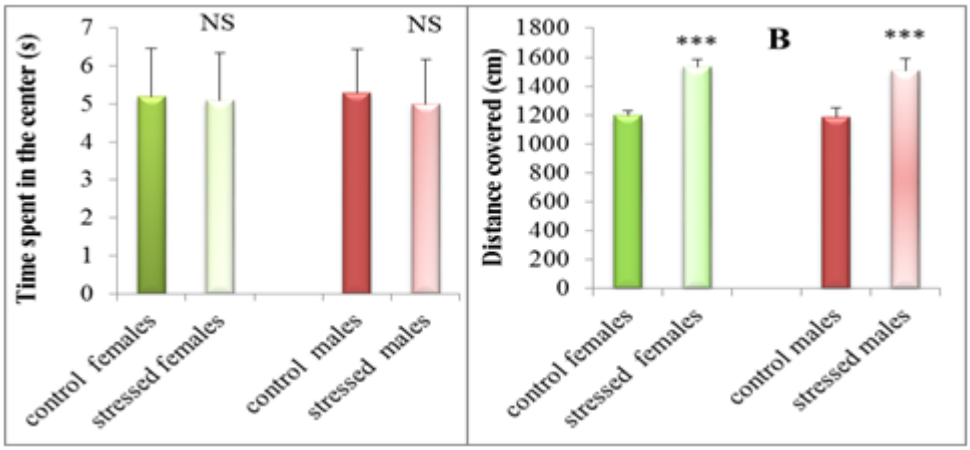

Figure 4: Effects of chronic restraint stress on behaviour of the offspring evaluated in the open field test in post natal day 45. Time spent in the center (A), distance covered (B) respectively. (m ± SD; * p < 0.05; **p < 0.01; ***p < 0.001)

5. Discussion

Numerous study have been carried out to understand the role of various lifestyle factors contributing to stress and the development of the anxiety-like and the appearance of depression-like behaviour **[3]**. The perturbation in sexual behaviour and the disturbances of the oestrus cycle **[21]**.

This experimentation showed that chronic restraint stress reduced open-arms entry in the EPM, increased immobility in the FST with elevation of plasmatic concentration of progesterone. Results met in the test of EPM suggesting elevated anxiety-like behaviour. In addition, increased immobility in the FST indicating exacerbated despair- like behaviours, suggesting that pathological changes in mood-regulating system might be induced by chronic restraint stress CRS. Stress generates behavioural modifications, and it would be responsible, at the Man, many psychiatric disorders such as the depression or the disorders related to the anxiety **[22]**. Researchers **[9,23]** noted that chronic restraint stress induced anxiety- and depression-like behaviours in rodents, reduced open-arms entry in the EPM which indicate a general motor activity **[24]**, consistent with our results. However, other studies have not confirmed such changes after CRS **[10, 25]**, but Contradiction in results might be attributed to the total duration of CRS, to the experimental procedures (e.g., light–dark phase; during restraint), and genetics factors (sex of the animal), all these might affect behavioural outcomes after CRS **[22]**. Gustavo et al. (2006) **[24]** not found such differences between protocols in the appearing of anxiety when he made a comparison between the acute, sub chronic and chronic stress, all protocols of stress were able to induce significant anxiety levels in elevated plus maze test.

We also demonstrated that restraint stress induced an elevation in plasma concentration of progesterone that can be mediated solely by adrenal gland. The same result was mentioned by Romeo et al. (2004) **[26]**.This result confirms the interaction between ovarian and adrenal steroids and the release of gonadotropin CRH **[27]**, to release ACTH, corticosterone **[28]** and adrenal progesterone **[29]**. Also Guillermo et al. (2011) **[30]** showed after application of

restraint stress an elevation in the level of progesterone. CRH, the main regulator of the HPA axis it controls the use of proopiomelanocortin peptide, by reducing the synthesis of hypothalamic GnRH by redirecting to synthesize ACTH necessary to the maintenance of homeostasis in stressful situation **[31]**. Which result a decrease in pulsatile release of LH **[32]**, this process is independent of the stress-induced cortisol level **[33]**. However, prolonged enhanced secretion of cortisol contributes to the suppression of GnRH pulse frequency, but only in the presence of ovarian steroids **[34]**, and may negatively affect the reproductive function via actions at the hypothalamus (GnRH) as well as impairing LH release induced by GnRH **[35]**.

Studies on ovariectomized sheep indicated that psychological stress or increase in plasma cortisol during psychological stress **[36]** acutely reduces LH pulse amplitude by two mechanisms. First mechanism involves cortisol action via type II glucocorticoid receptor to inhibit pituitary responsiveness to GnRH, and second by changes of hypothalamic GnRH secretion (changes in GnRH pulse amplitude and pulse frequency). This reduction contribute to the elevation indirectly of progesterone. Also chronic heat stress has been shown to be associated with elevated serum progesterone concentration in cows **[37]**. And elevated progesterone values in sheep and cattle have been associated with depressed gonadotrophin release **[38]**.Therefore, the depressed luteinizing hormone surge in ewes exposed to chronic heat stress **[39]** could be due to elevated progesterone concentration. Other investigators previously have observed that swim stress can increase progesterone as well as corticosterone secretion. Although progesterone has been considered only as a female reproductive hormone, elevated levels of plasma progesterone accompany the increase in corticosterone after stress in male rats **[40]** and male humans **[41]**. Stress-induced progesterone secretion in male and female rats is derived from the adrenal gland, because the response is abolished after adrenalectomy **[40]**.

Receptors for CRH are identified in most of the female reproductive tissues including the ovary, uterus and placental trophoblast **[42]** .And there is abundant evidence that the gonads affect the way that the HPA axis responds to stress. Van Lier et al. (2001b) **[43]** evaluated the presence of oestrogens receptors in sheep adrenal glands. Ovarian steroids have been found to increase HPA-axis activity, enhance the HPA-axis response to psychological stress, and sensitize the HPG-axis to stress-induced inhibition inhuman and rhesus monkey **[44]**.

Increasing of the distance covered in the open field test after weaning can be explained by the Hyperactivity of the offspring (locomotors). That is associated with a permanent hyperactivity of the HPA axis caused by a disturbance of serotoninergic and dopaminergic system in the central nervous system **[45]**. These changes could be mediated by in utero exposure of the developing brain to elevated levels of maternal glucocorticoids (GCs) secreted during HPA axis activities in mother by stress. That can cross the placenta barrier and reach the developing fetal brain **[46]**. Which they could affect the maturation of the fetal HPA axis and program the responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis of the offspring **[47]**.

Although, other studies report that prenatal stress induced reduction in locomotion **[48]**. An increase in the levels of GABA neurotransmitter in the hypothalamus and the bed nucleus of the stria terminalis seem to be responsible for these disturbances **[49]** by causing depressive disorders at the adulthood.

6. Conclusion

Pregestational stress can affect the physiological state of the animal and the neurobehavioural development of the offspring like the gestational stress. This experiment probably put some tracks values especially for the transmission over generations of cognitive and behavioural damages.

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