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Neurobehavioral Effects of Dexamethasone (Inhibition of Adrenal Axis) in Male Mice *Mus musculus*

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Abstract: In this study we have evaluated and tested the effect of dexamethasone on the neurobehavioral aspect in male's mice. One dose 0.1 mg of dexamethasone was injected during the first 10 days of the period of experimental protocol. The animals are divided into two experimental groups (n=6): control mice and treated mice by DEX. These mice were undergone to behavioral tests: forced-swimming test (FST), elevated plus maze (EPM), tail suspension test (TST) and sucrose preference intake test. The results of our study shows that treated mice by DEX suffered from anxiety (In behavioral tests).

Key words: Mice · Behavioral tests · Dexamethasone (DEX) · Anxiety

INTRODUCTION

Stress and anxiety are now recognized as major health problems. Several expressions reflect a state of tension, uneasiness and discomfort more or less accentuated. They are often confused in everyday language [1].

If anxiety disorders are identified since the nineteenth century, the stress-related anxiety has emerged in recent decades and is constantly increasing. The current organization of our society generates a lot of stress that sounded on the psychological balance and well-being. More and more patients seek help from professionals. The charges taken of anxiety disorders are mainly psychological and imply that the subject acts against its symptoms and consequences [2, 3].

The need to study emotions in humans has led to the development of much research in animals. However, a credibility problem indeed, emotion and complex are generally defined in humans by a strong psychological component. Thus, anxiety is defined as an emotional state characterized by feelings of anxiety, insecurity, physical and mental disorders, waiting danger before which or is powerless [4].

The tests used to assess the state of anxiety in rodents (State anxiety) are classified into two categories based tests natural aversions (Or not put up tests) and tests based on learned aversions (Or tests packaged). Unconditioned tests are based on the innate and spontaneous reaction of the animal in a situation anxiety while packaged tests require a learning phase or packaging in which a neutral stimulus (Conditioned fear protocols) or reward (Food, drink or drug; conflict protocols) is associated with an aversive stimulus (Electric shock eg) [5, 6].

Our study aims to assess the effect of stress on the development of anxiety behavior in mice by injecting a synthetic glucocorticoid hormone (Dexamethasone). This drug from the family of steroids is a derivative of the natural cortisone. It has the same anti-inflammatory activity that the hormone with fewer effects. It is used in many inflammatory diseases or allergies, asthma, sinusitis, ear infections, certain cancers where he fights against cell proliferation, prevention of graft rejection by decreasing immune responses, multiple sclerosis and rheumatic fever. It is sometimes used illegally to other doping substances and anabolic in farms to fatten animals more quickly, increasing the protein content of the meat,

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while decreasing lipid levels. Therefore, this product is prohibited for sports and racing animals and can induce a positive doping test [7].

MATERIALS AND METHODS

Biological Material: The animals used throughout this work are white male mice of the Swiss strain from the Pasteur Institute of Algiers. Upon arrival at the pet, mice are placed in collective cages (3-4 animals per cage) in an informed pet in a 12h cycle: 12h and maintained at an average temperature of 20 ± 4°C and relative humidity 50-70%. The cages used are plastic having a stainless steel lid, provided with bottles. A thick layer of sawdust is placed at the bottom of the cages and renewed every 2 days. The mice were fed daily with food, in the form of commercial origin stick, "Consist of pellets made from corn, bran, middling's, soybean and vitamin mineral supplement and receive water.

Animals have free access to water and food throughout the experiments. After an adaptation period of three weeks of acclimatization to rearing conditions of our animal before the experiments. The animals are isolated and handled and weighed daily to familiarize the experimenter. All tests are performed during the daytime phase (8h-15h).

We selected 12 males according to weight (Between 32 to 44 grams) and we divided them into two experimental groups: a control group, a group treated with dexamethasone (DEX).

Injected Substance: Dexamethasone is a glucocorticoid hormone synthesis. It has an anti-inflammatory and immune-modulators effect. We injected a dose of DEX 0.1 mg [8] for each mouse during the first 10 days of the period of experimental protocol, after 10 days we repeated behavioral tests (FST, TST, EPM,).

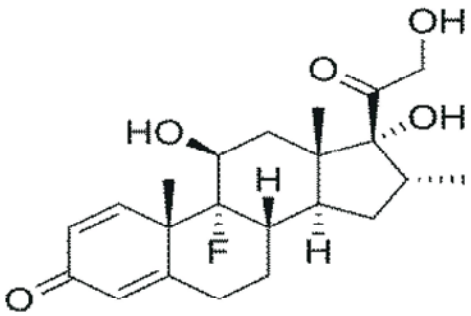

Fig. 1: Chemical structure of Dexamethasone (DEX)

Experimental Protocol

Behavioral Tests

Forced Swimming Test (FST): The FST or (Forced Swimming Test) is a behavioral model to predict the efficacy of antidepressant therapy [9, 10]. This animal model used both in rats than in mice, however, has different procedures depending on the species used. It consists of placing mice in an aquarium 20cm in diameter and 40cm deep filled with clean water 25cm deep (Temperature between 23 and 25°C). The test lasts 6 minutes, but only the last 4 minutes of the test are used to record the swimming time. The variables are measured on the FST: Immobility time, Swimming time, climbing time.

Elevated plus Maze (EPM): The elevated plus maze test is used to measure the degree of anxiety in rodents. The device is cross-shaped and has a high height of 40 to 60 cm from the ground. It consists of a central portion (10 × 10 cm), two protectors open arms without walls (50 × 10 × 50 cm) which oppose two other arm, perpendicular to the previous ones, farms by walls lasts test 5 minutes and begins when the rat is placed in the center of the maze, facing an open arm. This procedure is the one originally used by Pellow *et al*. [11]. Other authors place the animal faces a closed arms and these are preliminary observations that lead us to choose the first option.

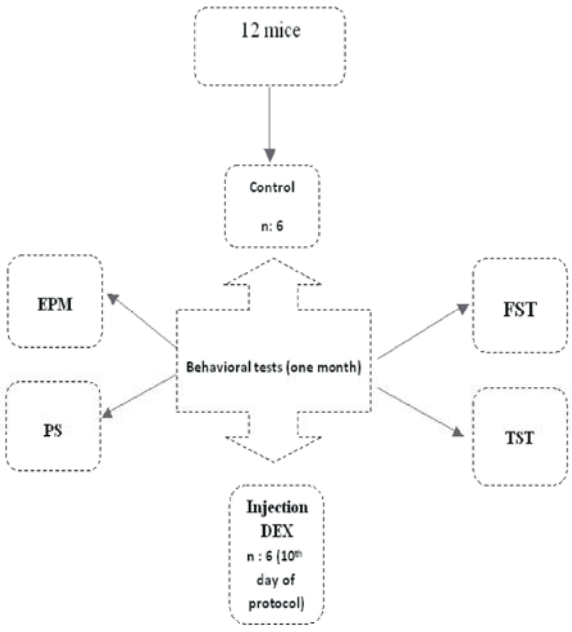

Fig. 2: Experimental protocol

During this test, the measured variables are: Time spent in the center (Sec); Time in the open arms (Sec); Time in closed arms (Sec); Entries into the open arms; Entries in the closed arms; Number entries in the center [11-13].

Tail Suspension Test (TST): The tail suspension test originally developed by Steru and collaborators in Steru *et al*. [14] measuring the immobility of the animal. This test is performed for the measurement of muscle strength of the mouse. The mechanism used is formed of a cotton thread stretched between two wooden supports. The front legs of the young mice are brought into contact with the wire 40 cm from the ground, a tape is placed at the end of the caudal part of the animal, making it possible to suspend it by the tail to a videotaped during hook 6min. The mice will try to escape this demanding situation in a much more energetic and long than would a depressed mouse that quickly resign. During the test 6min, the mice alternate agitation and immobility phases, they struggle vigorously early in the test, then gradually end up giving up. The duration of immobility can determine their resignation threshold, the measured variable is the length of suspension (Time in seconds) using a stopwatch [15,16].

Sucrose Preference Test: All of the mice were submitted to 48 h of forced exposure to 1% sucrose solution in order to habituate to it Bourin *et al.* [17] during which sucrose solution was the only fluid available for consumption, followed by two days of free access to food and water. After this, the rats were submitted to water deprivation for 16 "h" prior to performing the sucrose preference test; baseline test at day zero. The sucrose preference test was performed in the rat's home cage: two pre-weighted bottles, one containing tap water and another containing 1% sucrose solution, were presented to each rat. The bottles were weighed again after 1 "h" and the weight difference was considered to be the rat intake from each bottle. The sum of water and sucrose intake was defined as total intake and the sucrose preference was expressed as the percentage of sucrose intake from the total intake following the formula: % sucrose preference= sucrose intake X100/total intake.

Statistical Analysis: Data are presented as mean ± SEM. Data were analyzed by one-way ANOVA and test t of Student. Results were considered significant at $p < 0.05$. Graph Pad Prism 5 for windows version 5.01 was used to do the analysis.

RESULTS

Forced Swimming Test Parameters (FST): wimming time (sec), Immobility time (sec) and climbing time (sec) in control and DEX group.

We used the student's t test. The results of (The histogram A) show that the time to swim in the controls is higher than treated with DEX. The analysis time of swimming showed no significant difference (R squared = 0.1090, M = -14.33).

The results of (the histogram B) show us that the time of immobility in controls is lower than treated with DEX. Analysis of immobility time showed no significant effect (R squared = 0.1391, M = -22.67).

The results of the graph (C) we show that the climbing time in controls was lower than treated with DEX. The analysis of the climbing time showed no significant effect (R squared = 0.1469, M = 37).

The Elevated plus Maze (EPM) Test: Elevated plus Maze (EPM) test parameters in control and DEX group: (A) time spent in closed arms, (B) number of entries in the closed arms (C) time spent in center device.

Time Spent and Number of Entries in Closed Arms: We used the student's t test. The results obtained (Histogram A) show that the time spent in AF in the control of the device is higher than that of treaties by DEX. The histogram B shows that there is an increase in number of entries the closed arms relative to controls treated with DEX. Analysis of the time spent in closed arms revealed no significant difference (R squared = 0.01909, M = 7.667). While the number of entries into the LF; the analysis indicates that there is a significant difference (R squared = 0.9490, M = 7.333, $P < 0.05$).

Time Spent in Open Arms: We used the student's t test. The results obtained (Histogram C) show that the time spent in the open arms of the device in the controls is lower than treated with DEX. The analysis of the time spent in the open arms showed no significant difference (R squared = 0.05401, M = 9).

The results obtained (Histogram D) we show that the time spent in the center of the device in the controls is lower than treated with DEX.

The analysis of the time spent in the center revealed no significant difference (R squared = 0.06913, M = -16.67).

Tail Suspension Test (TST): Tail suspension test parameters in control mice and DEX treated (A): mobility time (sec), (B): Immobility time (sec).

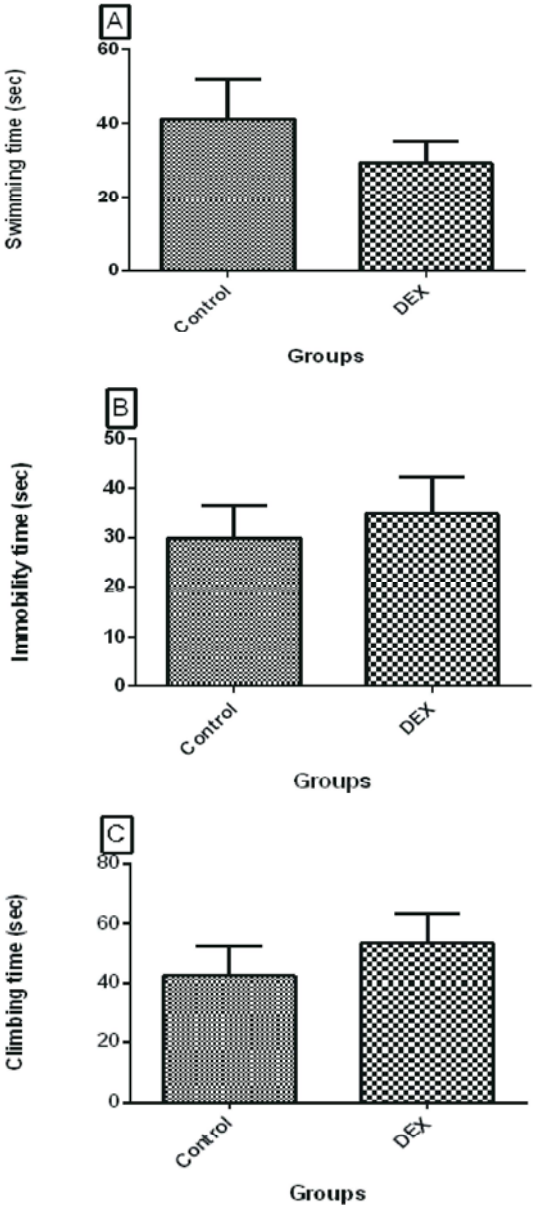

Fig. 3: Evolution of forced swimming test parameters: Immobility time (A) (sec), Swimming time (sec) (B) and climbing time (sec) (C) in control and DEX group

We used t-test results of Student. The results obtained (Histogram A) show that the mobility of time in control is higher than treated with DEX.

The results of (Histogram B) we show that the immobility time in the DEX is higher to compare as control.

Sucrose Intake: Sucrose intake parameters in control mice and treated with DEX.

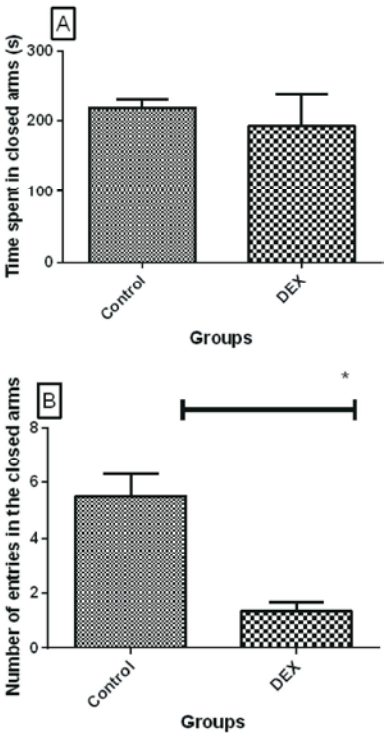

Fig. 4: Elevated plus Maze (EPM) test parameters in control and DEX group: (A) time spent in closed arms, (B) number of entries in the closed arms

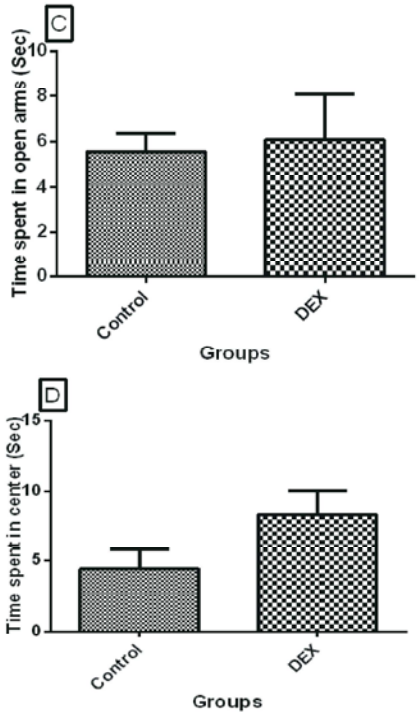

Fig. 5: Elevated Plus Maze (EPM) test parameters in control and DEX group: (C) time spent in open arms (sec), (D) Time spent in center device (sec)

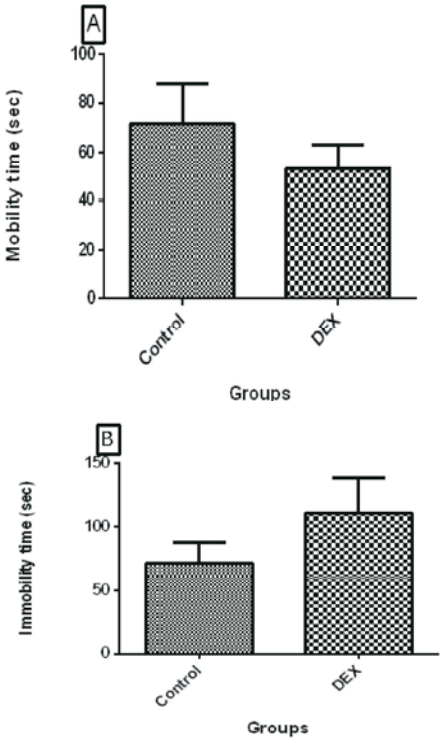

Fig. 6: Tail suspension test parameters in control mice and DEX treated (A): mobility time (sec), (B): Immobility time (sec)

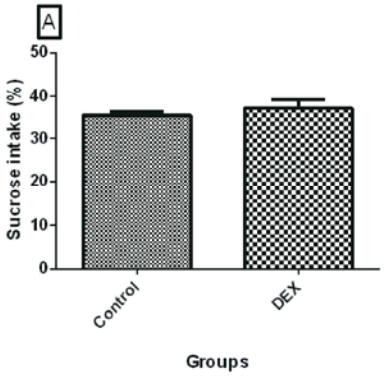

Fig. 7: Sucrose intake (%) (A) parameters in control mice and treated with DEX

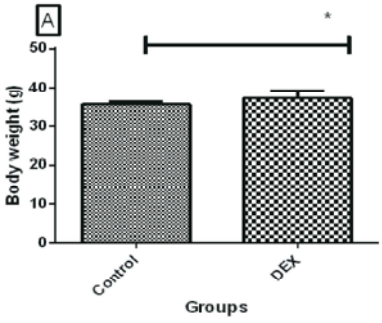

Fig. 8: Body weight (A) in control and DEX treated mice

We used the student's t test. The results obtained (Histogram A) show that the preference sweet administered to the DEX group treated is higher than that of control The analysis revealed no significant difference (R squared = 0.6810, M = 3.047).

Body Weight: Body weight in control and DEX treated mice We used t-test results of Student. The results obtained (histogram A) show that the weight of control is lower than treated with DEX. We note that there is a weight gain in the mice treated with DEX. The weight analysis indicates that there is a significant difference (R squared = 0.9235, M = 4.333, P <0.05).

DISCUSSION

Anxiety is a concept that has been analyzed from several perspectives in health and behavioral science [18, 19]. It would be a physiological signal that reflects the mobilization of the body for confrontation. It can be induced by extreme stimuli, with the possibility of achieving the life of a subject, or stimuli in a less intense gravity. In addition, the state of anxiety can be temporary or chronic relatively [20, 21].

Note, however, that anxiety results in temporary changes in the emotional state of an organism as a sudden apprehension and concerns accompanied by increased activity of the sympathetic autonomic nervous system and hypothalamus axis and adrenal in response to an internal or external stimulus[22].

Fear and anxiety are adaptive mechanisms to alarm the body. The anxiety becomes pathological when it is inadequate when it is excessive and uncontrollable [23]. To establish the pathological features of anxiety, a commonly used criterion is whether the emitted behavioral response is exaggerated or disproportionate to the real situation [24, 25].

There are environmental factors interact with biological factors specific to individuals as their neuronal functioning [26] and genetics, thus modulating their susceptibility to experience anxiety [27,28]. This interaction between environmental and biological factors are also in animals [29]. These conditions train frequently behavioral changes in laboratory animals and produce at home in anxious behavior [30, 31].

The level of anxiety in male mice was evaluated through behavioral tests in an elevated cross maze (EPM), sucrose intake test (preferably sweet), while the level depression is assessed using the forced swim test (FST) and the tail suspension test (TST). The intraperitoneal

injection of dexamethasone (DEX) 0.1ml / kg for 10 days a single injection was made in the 1st day which induced a remarkable anxiety in previous tests [32, 33].

Dexamethasone belongs to a class of medicines named corticosteroids. It can be used in the treatment of a wide range of ailments. It can be prescribed to replace cortisone in patients who are deficient in cortisone. In addition, dexamethasone can be used to treat many conditions including respiratory diseases (Such as asthma), skin diseases, severe allergies, certain eye diseases, rheumatoid arthritis, inflammatory bowel disease, some hematological disorders and certain forms of cancer. Inflammation plays a role in these diseases. Dexamethasone acts by reducing inflammation [34].

The results of our study showed that intraperitoneal injection of dexamethasone that applied to cause behavioral changes in the mice proved by the following tests: In the forced swim test (FST) we notice a decrease in swimming time, increase of climbing time and immobility time in treated DEX (Figure3) [36-37].

On the test elevated plus maze (EPM). (Figures 4, 5). Note that the mice are placed or take refuge in the closed arms and have fear of heights when they are less anxious they circulate freely in the open arms of the device [38].

The tail suspension test (TST) shows an increased immobility time of mice treated with DEX relative to the control group by cons we notice a decrease in the mobility of time in mice treated with DEX. (Figure 6).

The last two behavioral tests (FST, TST) confirm the mouse state of depression which sudden treatment with DEX [39].

Regarding sucrose test (Sweet preference) the preference sweet administered to the DEX group treated is higher than that of control (Figure 7).

The fact that anhedonia is one of the basic criteria for diagnosis of major depression and can be induced in mice by administration of dexamethasone, hence the idea that the corticosteroid plays an important role in neurobiology of depression. For example, chronic administration of corticosterone reduces the threshold current for the hypothalamic self-stimulation [40].

For the weight of the mice we found weight gain among mice treated with DEX compared to control group, the weight increase is owed has the effect of dexamethasone as a synthetic glucocorticoid hormone (Figure 8). DEX has an effect anti-inflammatory and immunosuppressive.

The dexamethasone is sometimes used illegally to other doping substances and anabolic in farms to fatten animals more quickly, increasing the protein content of the meat, while lowering lipid levels [41]. Immunosuppression by glucocorticoids is mediated via a direct cytolytic effect by inhibiting the function of lymphocytes, or indirectly through suppressor soluble mediators [42].

Glucocorticoids are steroids which act on the protidic metabolism and carbohydrate. Natural glucocorticoids are cortisone and hydrocortisone (Or cortisol). Synthetic glucocorticoids are either short effects (Prednisone) or intermediate effects (Paramethasone) or prolonged effects (Betamethasone). Drugs are called steroidal anti-inflammatory when employed for this purpose. Dexamethasone is classified in the family of long-acting corticosteroids [43].

Stress affects the functions of the neuro-immune system, it induces inflammation in various parts of the brain against depression is correlated to immune system abnormalities [44-46].

According to our results the injection of dexamethasone caused a significant weight gain compared to the control group and behavioral tests have caused a depression for the forced swim test characterized by increased anxiety for the test of plus maze and increased mobility in the tail suspension test (TST) and some increase in the consumption rate of the sweet drink in sucrose test.

CONCLUSION

Our work aims to test a dose dexamethasone (DEX) on male mice to see if he had a neurobehavioral effect. After a well-defined experimental study our results showed the following findings:

- The intraperitoneal administration of 0.1 mg / kg exerted a neurobehavioral effect.
- Body weight showed a remarkable increase of mice injected by DEX.
- The results of our work show test level forced swimming (FST) which is used to measure and assess depression, decreased time to swim in the treated group and DEX climbing time increased and time of immobility. Therefore DEX caused an increase in the time of immobility.
- The results for the test of elevated plus maze (EPM), the mice are placed or take refuge in the closed arms and have fear of heights when they are less anxious they flow freely into the open arms of the device.

- However tail suspension test (TST) increased immobility time of mice treated with DEX relative to the control group by reduction of the mobility against time in mice treated with DEX.
- Regarding sucrose test (sweet preference) no difference between the two lots that witnesses and dealt with DEX.
- Finally, according to our results, the mice treated with DEX more behavioral tests have sudden anxiety but also the most outstanding in this experiment is the weight gain and the state of anxiety noticed what proves immunosuppressive effect of dexamethasone part glucocorticoid family.

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