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Assessment of neuropharmacological consequences induced by dexamethasone administration in rats model of neurodegenerative diseases

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Abstract: Stress is a well-known and frequently used term among present generation. It has been referred to the response of body to any challenge for a change. It is a natural process and our body is designed to cope with it. However, if stress becomes chronic, it can lead to mental health problems. Stress due to the prolonged administration of glucocorticoid is enabled to produce impressive alterations in rats model shoeing depressive like behavior. In this investigation; purpose was to study the impact of episodic treatment of dexamethasone with respect to behavioral changes in rats. It was hypothesized that repeated administration of dexamethasone could increase stress and thus, psychological stress leading to mood disorders and behavior deficits in rats. Rats were injected daily with DEX (10 mg/ml/kg, orally) and the different behavioral models of the animals were assessed. DEX-treated rats exhibited depressive behavior like greater time to start mobility in a novel environment, and elevated anxiety-like behavior in elevated plus maze. However, time spent in light compartment was shorter with repeated administration of DEX. From results it is demonstrated that the administration of DXM for weeks induced stress and consequently, induced a depression-like behaviors in rats models.

Keywords: Stress, dexamethasone (DXM), neurological disorders, behavioral paradigram manifestations.

INTRODUCTION

Stress, the term was introduced by (Selye, 1956) who relates it to a psychological or physical stimulus that threatens internal balance of physiological systems. Stress is any type of change that causes physical or psychological tension which results in the disturbance of the homeostasis of the body. This disturbance is restored by physiological or behavioral adaptive responses. These responses are facilitated by stress system, which includes central nervous system as well as periphery system (Chrousos, 2009). The development of antidepressants and research into their mechanisms of action has changed how we understand how neurons work and how depression is effectively treated. Antidepressant treatment for mental illness may have therapeutic effects by promoting useful moderating fluctuations in neural coordination. Thus a stressor is any stimulus that triggers body's physiological reaction to occur. It can be external such as weapon, environment or toxins, or internal such as one's perception of being in uncertain, fearful or threatening situation. The intensity of physiological reaction to stress depends on the type of stressor and is therefore, depends on an individual and situation (Peters *et al.,* 1998; Anderson *et al.,* 2019).

Two primary systems like sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are activated in response to stress. The SNS causes the adrenal medulla to release catecholamines and cortisol from the adrenal cortex. The paraventricular nucleus of the hypothalamus produces corticotropic-releasing factor (CRF), which stimulates the anterior pituitary gland to produce adrenocorticotropic hormone (ACTH). Adrenal cortex is subsequently stimulated by ACTH to create adrenal glucocorticoid (GCs), including cortisol (Mariotti, 2015). Through a negative feedback loop, the cortisol in turn prevents the creation of CRF. Elevated blood glucose levels are caused by the stimulation of lipolysis and glycogenolysis by the release of catecholamines and cortisol (Anderson, 2019; Schneiderman, 200; Kolcz, 2012). Life's stressful experiences damage serotonergic neurotransmission, which results in disorders like stress and depression. The effects of drugs and new stressors on behavior, neurochemistry and physiology are amplified by chronic stress. Katz and Colleagues were the first to use a chronic stress model to test antidepressant drug in early 1980 (Katz *et al.,* 1981). Depressive phenotypes reported after chronic stress includes reduced weight gain (Willner *et al.,* 1987) and altered monoamine levels (Rowlett *et al.,* 1991). Dexamethasone, a synthetic corticosteroid that can cause a variety of mood disorders, including depression and mood psychosis, is toxic to certain populations of hippocampal and striatal neurons.

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The body keeps glucocorticoid levels within limits through a feedback mechanism, and disturbances at any level affect other components through the feedback loop of the HPA axis. Dysregulation of the HPA axis can have adverse effects on health, such as chronic stress (Millar, 2002). Number of studies has shown that depression is linked with the abnormal functioning of HPA-axis and elevated cortisol levels (Yasir *et al.,* 2021; Duval *et al*., 2006). It is well known that exogenous glucocorticoid and endogenous elevation of cortisol are associated with mood disorders and cognitive dysfunctions (Yasir *et al*., 2021). HPA axis suppression after exogenous glucocorticoid; Dexamethasone (DEX) is often associated with depression in humans. DEX binds to pituitary glucocorticoid receptors, activating a negative feedback loop and suppressing ACTH expression. The dexamethasone inhibition test, commonly used to diagnose Cushing's syndrome, has also been used experimentally to test for a dysfunctional HPA response in depressed patients (Carroll, 1982). The purpose of the study was to determined the impact of synthetic glucocorticoid; Dexamethasone administration for weeks with respect to behavioral changes in rats. It was hypothesized that repeated administration of dexamethasone could increase psychological stress thus, leading to mood disorders and behavior deficits in rats.

MATERIALS AND METHODS

Animals

Male rats, (180-220gms) were buying from Dow University of health sciences, Karachi. All animal experimental work was done under the supervision of departmental ethical board. Before the experiment, all the rats were placed under 12 hours dark and light conditions, controlled animal room temperature (25±2°C) with standard rats diet and water.

Drugs

All used drugs used were buying from Sigma Aldrich (USA).

Experimental design

Male rats (24 rats) were equally halved into two equal groups; (1) Saline administrated and (2) DXM administrated rats. Control group were orally administered 0.9% saline and test group were administered with dexamethasone (10mg/ml/kg) consecutively for 14 days. Change in growth rate and food intake by the rats were monitored after 24 hrs of first day and then after 1st and 2nd weeks of drug administrations. Assessment of all parameters were determined on next day of 1st and then weekly of DXM treatment. Activity in familiar environment was determined on alternate days of drug treatment

Behavioral assesment

Food intake

All rats of equal weights were placed in individual cages. They were fed with a weighed amount of freshly prepared standard Laboratory diet containing 30% protein, 30% fat and 40% carbohydrates. The food was placed in each of the cages and food intake was monitored after 24 hrs of 1st and then weekly treatment.

Growth rate

Change in growth rats was measured to determined the impact of drug or diet and growth. All the rats were weighed before the beginning of the experiment, and then regularly to monitor the changes in the body weight after daily drug administration.

Activity box test

The activity box test is usually recommended to determine the activity in a familiar environment in the laboratory rodents. The home cages provide familiar environment to rodents. Its best and simple way to assist behavior that reflects alteration in the animal's physiology. A square shaped (26×26×26cm) perspex activity cage with a floor covered with saw dust is used in this study to determine the locomotory activity of rats. While the top of the cage is covered with lid.

EPM

The test illustrates the anxiety-related reaction; it is an elevated plus maze. Anxiolytic behavior was tested with a +-shaped instrument. Two of them measured 50 by 20 centimeters and were open, while the other two were closed. The center (10 x 10cm) and height (100cm) of each arm connected them to each other. Every animal was permitted to sit in the middle of the maze with all of its paws in order to gauge their response. Over the course of five minutes, the amount of time spent exploring and making open-arm entries was recorded.

MWM

Richard Morris created the Morris water maze test in 1981, and it is used to assess spatial learning (Morris, 1981). The device consists of a white circular pool with a diameter of 90 cm and a height of 60 cm, filled to a depth of 30 cm with regular tap water at 22±2ºC. The pool was divided into four quadrants and non-fat powder milk was added to disguise it. One quadrant had a hidden platform measuring 15 cm by 15 cm that was positioned 1 cm below the water's surface. Spatial signals concerning the rooms were positioned in a quiet room with a water-filled Morris maze for the spatial memory test. The setup of the equipment prevented the animal from seeing the researcher.

Ethical approval

Experiments were carried out according to a strict procedure and in a well-organized manner, using a detailed guide for the care and management of laboratory animals (Institute of Laboratory Animals Resource of Life Science, US National Research Council, 1996).Ethical approval was taken through Reference No. ASRB

06618/SC by Advanced Study and Research Board, University of Karachi.

STATISTICAL ANALYSIS

All data that were presented as Mean±SD. By two Way ANOVA (Repeated measured design) data of drug administration of control and test rats were analyzed. The Analysis software used was SPSS (version 17). The Newman-Keuls test was used for post-hoc comparison. The values i.e. $p<0.05$ is considered as significant.

RESULTS

Effects of administration of dexamethasone on food intake

Fig. 1 show the effect of dexamethasone episodic administration on food intake of rats for two weeks as observed after of 1st, 7th and 14th day of drug administration and then monitored weekly. As the values of food intake analyzed by 2 way ANOVA (repeated measured designing) the effect of Dexamethasone ($F=68.92$, df=1, 21, $p<0.01$) and the impact of repeated monitoring ($F=57.78$, df=1, 21, $p<0.01$) and the interaction between all the values ($F=78.01$, df=1, 21, $p<0.01$) was determined significantly. Newman Keuls test was used for the Post hoc analysis which revealed that Dexamethasone decreased food intake on single and well as on repeated administration in rodents. Significant decreased was found in food intake of DXM group rats after 7th ($p<0.05$) as well as 14th ($p<0.01$) day of administration. On repeated DXM administration, food intake was significantly decreased as compared to 1st day administration ($p<0.01$) on 14th day.

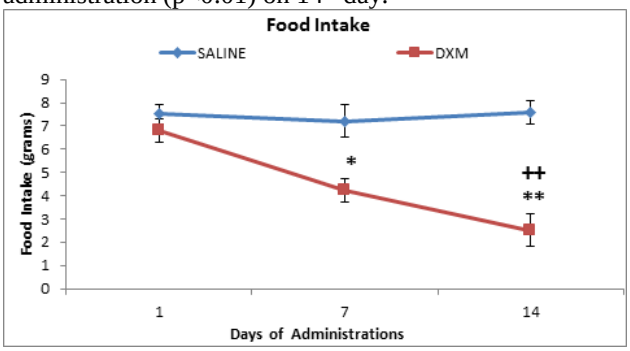

Fig. 1: Effects of Dexamethasone on Food Intake of rats
Values are means + SD (n=6) as monitored on alternate day of each drug administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1stday administration following two-way ANOVA (repeated measures design).

Effects of administration of dexamethasone on growth rate

Fig. 2 shows the effect of dexamethasone repeated administration on %change in body weight on rats for 14 days as they monitored on next day of 1stdrug and weekly administration. As the data analyzed by two-way ANOVA (repeated measured designing) the effect of days ($F=87.71$, df=1, 21, $p<0.01$), the effect of dexamethasone ($F=29.68$, df=1, 21, $p<0.01$) and the interaction between drug and days ($F=117.92$, df=1, 21, $p<0.01$) were found significant. Post hoc analysis by Newman Keuls test showed that administration of Dexamethasone decreased growth rate on repeated administration in rats as compared to saline administrated rats. Significant decreased was found after 7th ($p<0.05$) and 14th ($p<0.01$) day of administration. As compared to similarly administrated rats of 1st day of administration, growth rate decreased in dexamethasone administrated rats. Significant decreased was found after 14th ($p<0.01$) of administration.

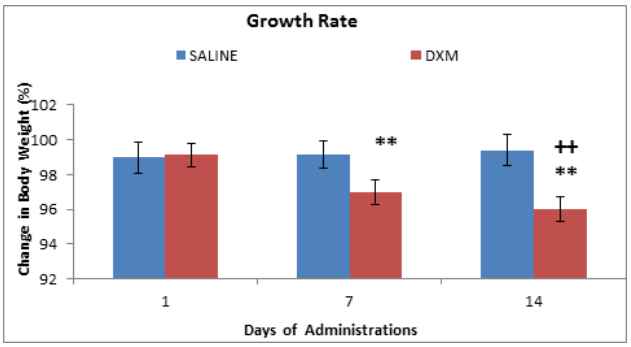

Fig. 2: Effects of Dexamethasone on growth rate of rats
Values are means + SD (n=6) as monitored on alternate day of each drug administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1stday administration following two-way ANOVA (repeated measures design)

Effects of administration of dexamethasone on home cage activity

Fig. 3 shows the effect of dexamethasone repeated administration on activity in a familiar environment (number of cage crossings) on rats for 14 days as they monitored after on next day of 1st drug administration and then on alternate days of each drug administration. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of days ($F=114.80$, df=1, 21, $p<0.01$), the effect of dexamethasone ($F=187.85$, df=1, 21, $p<0.01$) and the effect of interaction between all factors ($F=84.92$, df=1, 21, $p<0.01$) were found significant. Post hoc analysis by Newman Keuls test showed that administration of dexamethasone decreased number of cage crossings in familiar environment (home cage activity box) as compared to saline administrated rats on single as well as on all alternate day activity. Significant ($p<0.01$) decreased was found after 11th, 13th and 15th day of administrations. As compared to similarly administrated animals of saline or dexamethasone administrated rats from 1st day of administration, number of cage crossed decreased on in dexamethasone administrated rats. Significant ($p<0.01$) decreased was found after 11th, 13th and 15th day of administration.

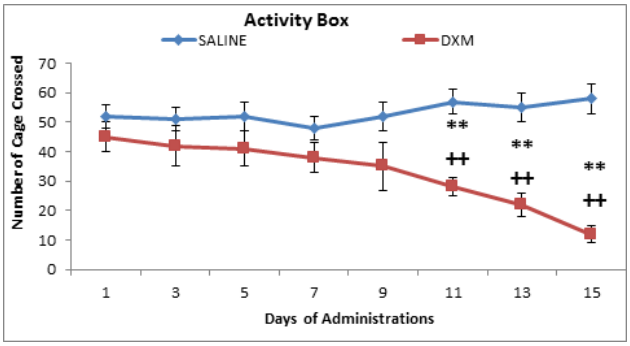

Fig. 3: Effects of Dexamethasone on activity in home cage of rats

Values are means + SD (n=6) as monitored on alternate day of each drug administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

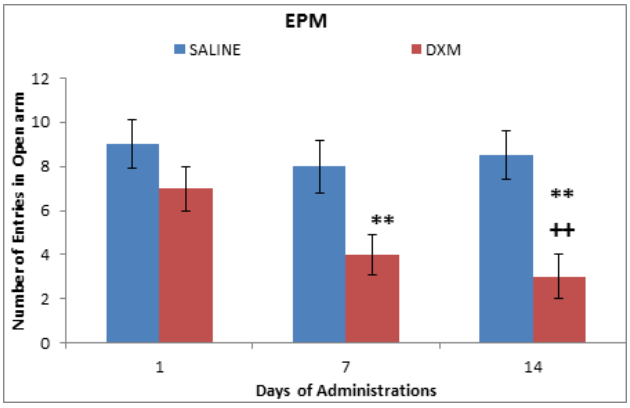

Fig. 4: Effects of Dexamethasone on activity of rats in EPM.

Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

Effects of administration of dexamethasone on EPM (entries in open arm)

Fig. 4 shows the effect of dexamethasone repeated administration on activity in elevated plus maze (number of entries in open arm) on rats for 14 days as they monitored after on next day of 1st drug administration and then monitored weekly. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of dexamethasone (F=182.91, df=1, 21, p<0.01) and the effect of repeated monitoring (F=141.34, df=1, 21, p<0.01) and the effect of interaction between Dexamethasone and days (F=88.45, df=1, 21, p<0.01) was found significant. Post hoc analysis by Newman keuls test showed that administration of dexamethasone decreased activity in elevated plus maze (number of entries in open) on single and on repeated administration in rats as compared to saline administrated rats. Significant decreased was found after 7th (p<0.05) and 14th (p<0.01) day of administration. As compared to similarly administered rats of 1st day of administration, entries in open arm decreased in dexamethasone administrated rats. Significant decreased was found after 14th (p<0.01) of administration.

Effects of administration of dexamethasone on EPM (time spends in open arm)

Fig. 5 shows the effect of DXM repeated administration on activity in EPM (time spent in open arm) on rats for 14 days as they monitored after on next day of 1st drug administration and then monitored weekly. As data analyzed by 2 way ANOVA (repeated measured designing) the effect of dexamethasone (F=98.78, df=1, 21, p<0.01) and the effect of repeated monitoring (F=128.75, df=1, 21, p<0.01) and the effect of interaction between all factors (F=105.81, df=1, 21, p<0.01) was found significant. Post hoc analysis by Newman keuls test showed that administration of dexamethasone decreased activity in an elevated plus maze (time spent in open arm) as compared to saline administrated rats on single and on repeated administration. Significant (p<0.01) decreased was found after one and two weeks of administration. As compared to saline or dexamethasone administered rats from 1st day of administration, number of time spent decreased on in DXM administered rats. Significant (p<0.01) decreased was found after 14th day of administration.

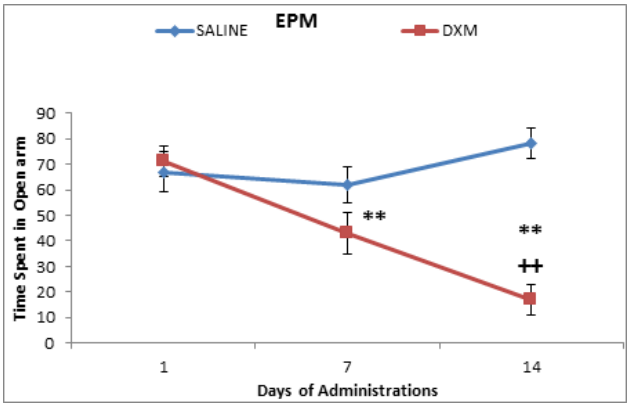

Fig. 5: Effects of Dexamethasone on activity of rats in EPM

Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design)

Effects of administration of dexamethasone on MWM (latency time post 1 hr)

Fig. 6 shows the effect of dexamethasone repeated administration on activity in Morris Water Maze Test Post 1hr (latency time) of drug administration for 14 days as

they monitored on next day of 1st drug administration and then monitored weekly. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of dexamethasone ($F=66.19$, $df=1, 21$, $p<0.01$) and the effect of repeated monitoring ($F=82.15$, $df=1, 21$, $p<0.01$) and the effect of interaction between all factors ($F=34.81$, $df=1, 21$, $p<0.01$) was found significant. Post hoc analysis by Newman keuls test showed that administration of dexamethasone increase latency time required by animal to start the movement on single as well as repeated administration as compared to saline administrated animals. Significant increase was found after 7th ($p<0.05$) and 14th ($p<0.01$) day of administrations. As compared to similarly administrated rats from day 1, administration of dexamethasone increase activity on repeated administration. Significant ($P<0.01$) increase was found after 14th day of administration

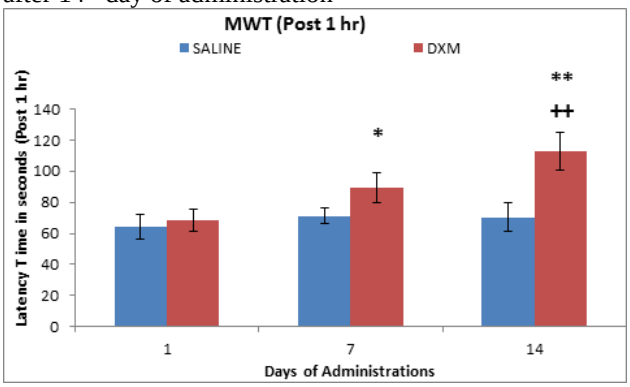

Fig. 6: Effects of Dexamethasone on activity of rats in MWM

Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design)

Effects of administration of dexamethasone on MWM (entries post 1 hr)

Fig. 7 shows the effect of Dexamethasone repeated administration on activity in Morris Water Maze Test Post 1 hr (entries) of drug administration for 14 days as they monitored on next day of 1st, 7th and 14th day of DXM administration. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of dexamethasone ($F=56.23$, $df=1, 21$, $p<0.01$), the effect of repeated monitoring ($F=94.31$, $df=1, 21$, $p<0.01$) and the effect of interaction between all factors ($F=55.49$, $df=1, 21$, $p<0.01$) was found significant. Post hoc analysis by Newman keuls test showed that administration of dexamethasone decreased activity Morris Water Maze Test (entries) as compared to saline administrated rats on single as well as on repeated administration. Significant ($p<0.01$) decreased was found after one and two weeks of administration. As compared to similarly administrated dexamethasone rats from 1st day of administration, number of entries decreased in dexamethasone administered rats. Significant ($p<0.01$) decreased was found after 7th as well as 14th day of administration.

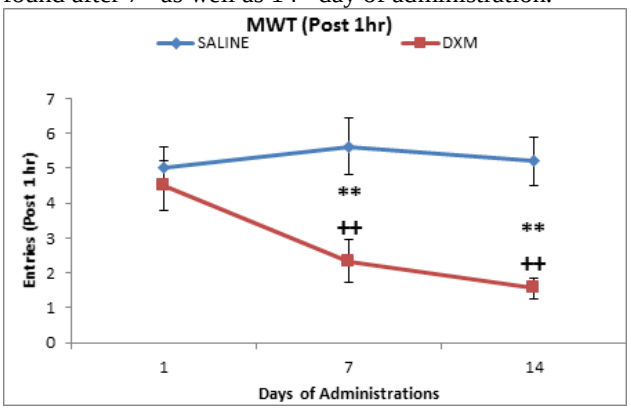

Fig. 7: Effects of Dexamethasone on activity of rats in MWM

Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design)

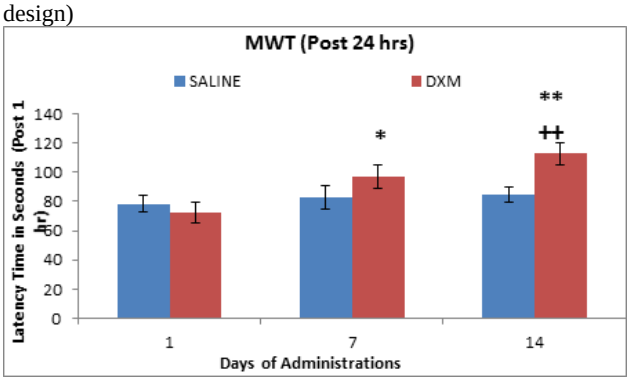

Fig. 8: Effects of Dexamethasone on activity of rats in MWM

Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

Effects of administration of dexamethasone on MWM (latency time post 24 hrs)

Fig. 8 shows the effect of dexamethasone repeated administration on activity in Morris Water Maze Test Post 24 hrs (latency time) of drug administration for 14 days as they monitored on next day of 1st drug administration and then monitored weekly. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of dexamethasone ($F=.65$, $df=1, 21$, $p<0.01$) and the effect of repeated monitoring ($F=81.87$, $df=1, 21$, $p<0.01$) and the effect of interaction between all factors ($F=51.49$, $df=1, 21$, $p<0.01$) was found significant. Post hoc analysis

by Newman keuls test showed that administration of dexamethasone increase activity in an MWM (latency time) as compared to saline administrated rats on single as well as on repeated administration. Significant increase was found after 1st week ($p<0.05$) and 2ndweeks ($p<0.01$) of administration. As compared to similarly administrated animals of saline or dexamethasone administered rats from 1st day of administration, latency time increased in dexamethasone administered rats. Significant ($p<0.01$) decreased was found after two weeks administration.

Effects of administration of dexamethasone on MWM (entries post 24 hrs)

Fig. 9 shows the effect of dexamethasone repeated administration on activity in Morris Water Maze Test Post 24hrs (entries) of drug administration for 14 days as they monitored on next day of 1st drug administration and then monitored weekly. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of dexamethasone ($F=43.91$, $df=1, 21$, $p<0.01$) and the effect of repeated monitoring ($F=61.55$, $df=1, 21$, $p<0.01$) and the effect of interaction between all factors ($F=77.16$, $df=1, 21$, $p<0.01$) was found significant. Post hoc analysis by Newman keuls test showed that administration of Dexamethasone decreased activity in MWM (entries) as compared to saline administrated rats on repeated administration but number of entries was increase on single administration. Significant ($p<0.01$) decreased was found after one ($p<0.05$) and two weeks ($p<0.01$) of administration. As compared to similarly administrated animals of saline or Dexamethasone administered rats from 1st day of administration, number of entries decreased on in Dexamethasone administered rats. Significant ($p<0.01$) decreased was found after 14thday of administration and ($p<0.05$) after 7th day of administration.

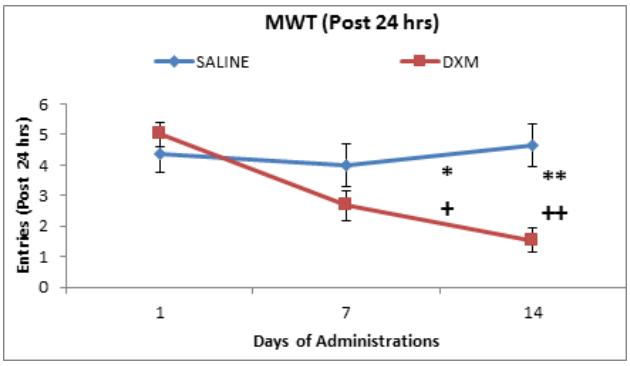

Fig. 9: Effects of Dexamethasone on activity of rats in MWM

Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *$p<0.05$, **$p<0.01$ from saline administrated animals; +$p<0.05$, ++$p<0.01$ from similarly saline or dexamethasone administrated animals of 1st day administration following two-way ANOVA (repeated measures design)

DISCUSSION

In this investigation we determined and explore the impact of single and episodic administration of dexamethasone on behavioral parameters such as growth rate, food intake and activity in a home activity box, elevated plus maze test and other behavioral test used to monitor the motor abnormalities in rats. Dexamethasone cause behavioral changes as well as Neuropathological changes in rats which is associated with the symptoms of depressive like behaviors in rats. The purpose of this investigation was to establish the effects of episodically administrated dexamethasone induce behavioral deficits as well as memory and cognitive impairment in animal model of rats. People tend to experience stress in everyday activities, for example before an exam or a presentation, or when they are experiencing something new or a novel environment. Stress is helpful to do everyday task; it keeps us in fight and flight mode that enables us to remain active and fulfill the required work. However, stress has been a consistent part of peoples' lives, and it is beginning to become one of the major concerns of this era. Impact of single episodic stress not longer exist as on other hand, the impact of episodic stress persist for a long time period and holds the capacity to cause damage to the body resulting in various disorders including psychological disorders and behavior deficits. The intensity of stress and its induced responses depend on the type of stressor and an individual that is experiencing it. Stress is also caused as a side effect due to chronic administration of certain drugs that are used for other purposes. Dexamethasone (DEX) on behavioral parameters in rats. 10mg/ml/kg/day DEX was orally administered consecutively for 14 days in which behavioral parameters were observed on next day of single and then weekly administrations. It has been reported that by continuous administration DEX has caused stress induced depressive like behavior in rats which was shown by the following different behavioral parameters that were used to analyze their behavior. As far as our results are concerned, the data shows that there was a slight decline in food intake on the 1st day following DEX administration than normal saline administered or control rats, then increased decline after the 7th day. Food intake was significantly decreased when monitored after day 14, whereas, it was increased in control rats; (fig. 1). The body weights of the DEX-administered rats; (fig. 2), were slightly increased than the control rats on the first day after administration, but decreased gradually after 7th day and significantly after 14th day. From previous study (Ferguson *et al.*, 2001), it has been reported that glucocorticoid administration for long period decrease body and brain weight in rats with neuro-behavioral changes. It has been revealed that depression is the mostly occurring neurological disease of this era. While significant progress has been made in treating treatment-resistant depression, it is still a

prevalent condition that affects approximately (Greenberg *et al.*, 1990; Rush *et al.*, 2006). In home cage activity, the activity by the rats increased a bit than control rats, but then continued to decrease after 7th and 14th day; (fig. 3). (fig. 4) shows that in plus maze, DEX decreased the activity of rats (number of entries in open arm) on single and on repeated administration in rats as compared to saline administrated rats and in (fig. 5), the time spent in open arm was almost with respect to saline administered rats after day 1, but significantly decreased till after day 14. In this study, the impact of acute and episodic administrated dexamethasone was determined on long term learning and memory. For this purpose, rat models of neurobehavioral deficits were investigated by MWM. Learning and memory is the most investigated parameters of cognitive functions determinations in rats. MWM is considered as most reliable method to determined both (Vorhees and Williams 2006). The MWM test probe trials are used to evaluate memory defects by analyzing time spent, distance traveled, time required to start to move and counts. Results from current study showed that the rats have some behavioral alteration in their ability for memory as well as learning after weekly administrations of DXM

CONCLUSION

The cumulative findings of present investigations revealed that behavioural impacts of rats that were administered with dexamethasone was decreased as compared to the controls rats in all the behavioral methods that were used. It was also find out that repeated administration of DXM induced greater impact of stress on rats as compared to acute administration of DXM. Therefore, it can be concluded that DEX induces stress and behavioral deficits in rats.

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