Neurological investigation of Cadmium induced oxidative stress and memory and learning impairment in neurodegenerative rat model

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ABSTRACT: Neurodegenerative diseases are a broad category of neurological disorders with a variety of clinical and pathological manifestations that affect specific subsets of neurons in specific functional anatomic systems. Oxidative stress complicates the pathophysiology of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Oxidative stress is caused by redox imbalances, which include either excessive production of reactive oxygen species (ROS) or antioxidant system dysfunction. Due to its high oxygen demand and abundance of peroxidation-susceptible lipid cells, the central nervous system is vulnerable to the effects of ROS. Cadmium is a neurotoxin with a high toxicity level and toxicity of Cadmium can be exacerbated by nutritional deficiencies. We have analyzed the behavioral changes in rats after receiving Cadmium on a regular basis. The home cage activity test, open field test, elevated plus maze test, and force swim test were used to assess the behavioral consequences and impairments in learning and memory of male rats who were given Cadmium (1.0 mg/ml/kg, orally) or saline daily. In the elevated plus maze, Cadmium-treated rats exhibited depressive behavior, such as increased time spent immobile in the open field and increased anxiety-like behavior. With increased Cadmium administration, however, time spent in the lit box decreased. Results indicate that prolonged exposure of rats to Cadmium induced stress, which subsequently led to depressive behavior.

Keywords: Cadmium (Cd), Neurodegenerative diseases Depression-Like, Anxiety-Like, Memory and learning impairment

INTRODUCTION

Neurodegeneration which refers to, in the case of tissues or organs, a process of losing structure or function. Thus, in the strict sense of the word, neurodegeneration corresponds to any pathological condition primarily affecting neurons. In practice, neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner (Przedborski S, Vila M, & V., 2003). This progressive neuronal cell death leads to various neurodegenerative disorders (NDDs) such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), brain trauma (BT), prion disease (PrD), etc., which can be differentiated based on their different pathological mechanistic pathways (Poddar, Chakraborty, & Banerjee, 2021). Oxidative stress is induced by imbalanced redox states, involving either excessive generation of reactive oxygen

species (ROS) or dysfunction of the antioxidant system. The brain is one of organs especially vulnerable to the effects of ROS because of its high oxygen demand and its abundance of peroxidation-susceptible lipid cells. Previous studies have demonstrated that oxidative stress plays a central role in a common pathophysiology of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease(Geon Ha Kim, Jieun E. Kim, Sandy Jeong Rhie, & author1, 2015).While aging is the key contributor to most of the NDDs, oxidative stress is the main factor for functional impairment during aging due to the oxidation of lipids, deoxyribonucleic acid (DNA), and proteins in presence of reactive oxygen or nitrogen species (ROS or RNS). Thus, it is not unreasonable to assume that enhancement in level(s) of ROS and/or RNS increase(s) the senescence of cells by secreting pro-inflammatory factors and enzymes followed by cellular degradation (Liguori, et al., 2018). The pathogenesis of several neurodegenerative disorders such as AD and PD is associated with the accumulation of misfolded proteins. The aggregation of these modified proteins can in turn trigger inflammatory response in the brain, which induces marked ROS release and subsequent OS(Liu, Zhou, Ziegler, Dimitrion, & Zuo, 2017) Cadmium (Cd) is a heavy metal that has received considerable concern environmentally and occupationally. Cd has a long biological half-life mainly due to its low rate of excretion from the body(Wang & Du, 2013). Cadmium, has no physiological function in the human body, is considered a bio-hazard. It is also considered to be a potent neurotoxin. The primary sources of cadmium exposure are diet and cigarette smoke. It has been postulated that nutritional deficiencies can increase the risk of cadmium toxicity. (Batool, et al., 2019). Prolonged exposure to Cd will cause toxic effect due to its accumulation over time in a variety of tissues, including kidneys, liver, and central nervous system (CNS), and peripheral neuronal systems. Cd can be up taken from the nasal mucosa or olfactory pathways into the peripheral and central neurons; for the latter, Cd can increase the blood brain barrier (BBB) permeability. However, mechanisms underlying Cd neurotoxicity remain not completely understood. Effect of Cd neurotransmitter, oxidative damage, interaction with other metals such as cobalt and zinc, estrogen-like, effect and epigenetic modification may all be the underlying mechanisms (Wang & Du, 2013). There are several sources of human exposure to Cd, including employment in primary metal industries, production of certain batteries, some electroplating processes (about 29% of year production), and consumption of tobacco products (Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. Working Group views and expert opinions, 1993). Exposure to Cd also severely affects the function of the nervous system (Wang & Du, 2013). With symptoms including headache and vertigo, olfactory dysfunction, parkinsonian-like symptoms, slowing of vasomotor functioning, peripheral neuropathy, decreased equilibrium, decreased ability to concentrate, and learning disabilities (Wang & Du, 2013).Cd-induced neurotoxicity might be caused by impaired neurogenesis, resulting in markedly reduced neuronal differentiation and axonogenesis, leading to neuronal cell death(Son, et al., 2011).

METHODS AND MATERIALS

ANIMALS AND CONDITIONS

Male Albino-Wister rats, weighing 180-220gm were purchased from Dow University, Karachi. Following strict protocol and assembled design with complete guide of care and use of laboratory

animals (Institute of Laboratory Animals Resource of life science, US national research council, 1996), the experiments and analysis were performed. Before the experiment, all the rats were placed under 12 Hours dark and light conditions, controlled temperature (22±2° C) and maintained on free access to rodent diet (standard) and clean tap water for familiarization for at least three days.

DRUGS

All chemicals and drugs that were used during study were purchased from Sigma Chemical Company (USA), Research Biochemical (RBI, USA), BDH chemicals pool (England) or Merck Company. Behavioral activity of each rat was monitored by different parameters and behavioral consequences were observed due to the action of specific drug.

EXPERIMENTAL PROTOCOL

24 male albino Wister rats were divided into two groups; (1) control and (2) test. Animals of control group were orally administered with 0.9% saline and animals of test group were administered with Cadmium (1.0 mg/ml/kg) consecutively for 28 days. Food intake and body weight were measured daily. All behavioral parameters were determined on next day of 1st, 7th 14th, 21st and 28thday of administration.

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 cage sand food intake was monitored next day of 1st day treatment and then regularly by weighing the amount of food left in the cages.

GROWTH RATE (BODY WEIGHT)

Body weights were measured to find out the effect 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.

OPEN FIELD TEST (OFT)

The assessment of exploratory locomotive activity in a novel environment was done by open field activity test. This test is performed to determine the behavioral consequence in a respective rat by the effect of drug. The present test consists the measuring of the activity of rats in an open novel environment, from which escape is prevented by surrounding walls. The open field apparatus used consist square area 76×76 cm with opaque walls 42 cm high. The floor of apparatus is divided by lines into 25 equal squares. To determine the activity, the rat is placed in the center square of box and its latency to move is measured and the number of square crossed with all four paws are scored for 5 minutes.

ELEVATED PLUS MAZE TEST (EPM)

Elevated plus maze test is one of the most widely used for measuring anxiety-like behavior in rodent models of CNS disorders and to test anxiolytic drugs. The test is based on natural aversion of rats for open and elevated areas. The apparatus is plus shaped and consists of two open arms, two closed arms of 10x50 cm and a center passage area. The height of the apparatus is 55 cm. The rat is placed on the center passage area and is allowed to move freely in the plus maze. The behavior is recorded that is expressed in terms of number of entries in open arms and time spent in open arms.

FORCE SWIM TEST (FST)

FST determine the antidepressant activity of drugs. The apparatus is consisting of water

filled transparent glass container with diameter 12cm and 22 cm height. Each animal allowed to swim in the apparatus containing 10cm water depth with maintained (25± 2 ºC) temperature. Swimming (struggling) time was recorded for the determination of antidepressant activity.

STATISTICAL ANALYSIS

All data that were presented as Mean± SD. By three waysANOVA (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 CADMIUM ADMINISTRATIONON FOOD INTAKE OF RATS

Figure 1 show the effect of Cadmium repeated administration on food intake on rats for 28 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 administration of cadmium ($F=63.38$, $df=1,21$, $p<0.01$) and the effect of repeated monitoring ($F=58.91$, $df=1,21$, $p<0.01$) and the effect of interaction between all factors ($F=41.77$, $df=1,21$, $p<0.01$) was found significant. Post hoc analysis by Newman Keuls test showed that repeated administration of cadmium decreased food intake in rats as compared to saline administrated rats. Significant decreased was found after 14th ($p<0.05$), 21st ($p<0.01$) and 28th ($p<0.01$) day of administration. As compared to similarly administrated rats of 1st day of administration, food intake decreased in Cadmium administrated rats. Significant decreased was found after 7th ($p<0.05$), 21st ($p<0.01$) and 28th ($p<0.01$) day of administration.

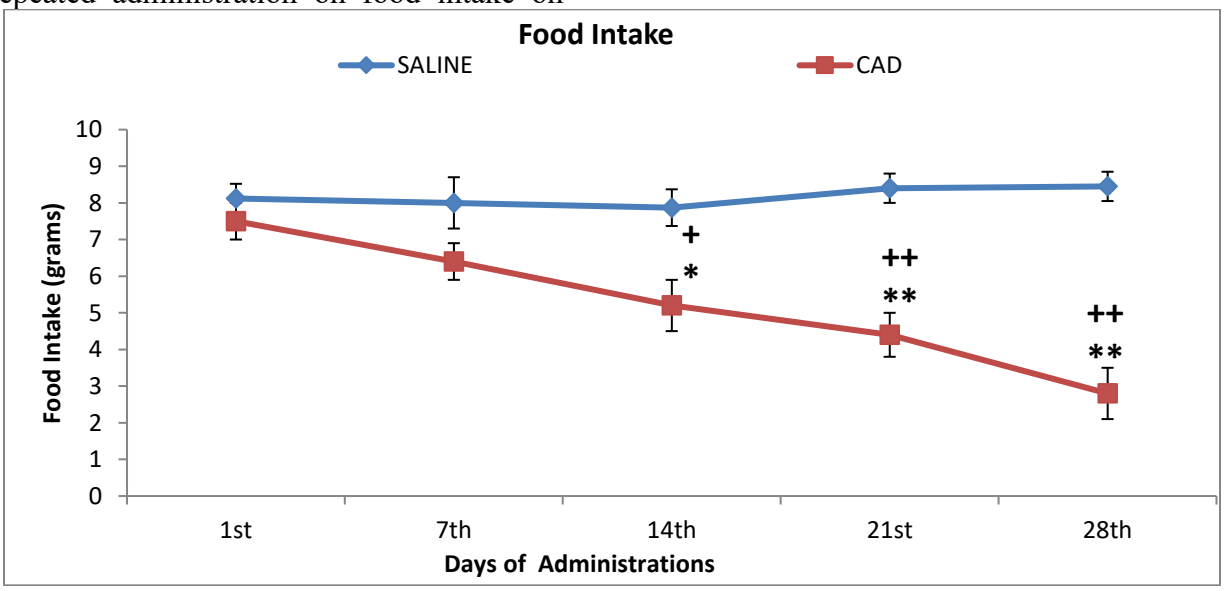

Figure 1: Effects of Cadmium on Food Intake of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *$p<0.05$, **$p<0.01$ from saline administrated animals; +$p<0.05$, ++$p<0.01$ from similarly saline or Cadmium administrated animals of 1st dayadministration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUMADMINISTRATION ON GROWTH RATE OF RATS

Figure 2 shows the effect of Cadmium repeated administration on change in growth rate on rats for 28 days as they monitored after on next day of 1st, 7th, 14th, 21st and 28th day of cadmium administration. As the data analyzed by two-way ANOVA (repeated measured designing) the effect of repeated monitoring ($F=54.59$, $df=1, 21$, $p<0.01$), the effect of cadmium administration ($F=68.22$, $df=1, 21$, $p<0.01$) and the effects of interaction between drug administrationand daysof monitoring ($F=72.18$, $df=1, 21$; $p<0.01$) were found significant.Post hoc analysis by Newman Keuls test showed that administration of Cadmium decreased growth rate on acute and on repeated administration in rats as compared to saline administrated rats. Significant decreased ($p<0.01$) was found after2nd, 3rd and 4th weeks of cadmium administration. As compared to similarly administrated rats of 1st day of administration, growth rate decreased in Cadmium administrated rats. Significant ($p<0.01$) decreased was found after 14th, 21st and 28th day of administration.

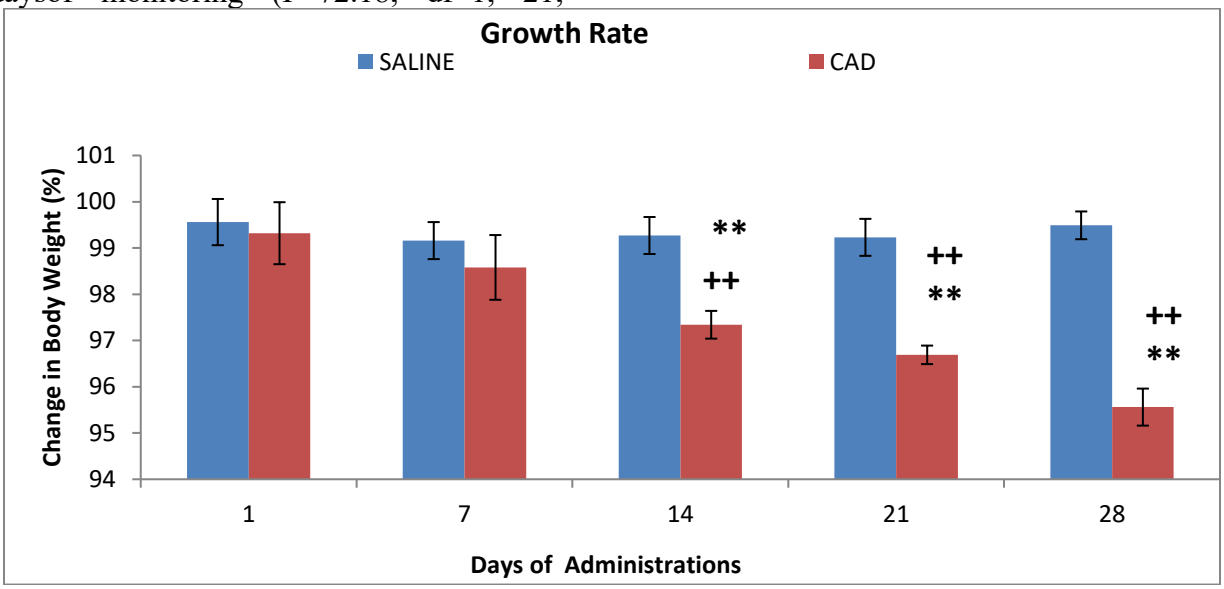

Figure 2: Effects of Cadmium on growth rate of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *$p<0.05$, **$p<0.01$ from saline administrated animals; +$p<0.05$, ++$p<0.01$ from similarly saline or Cadmium administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUM ADMINISTRATION ON OFT (LATENCY) OF RATS

Figure 3 shows the effect of Cadmium repeated administration on activity in novel environment (latency time) on rats for 28 days as they monitored after on next day of 1st drug administration and then monitored after 1st, 2nd, 3rd and 4th weeks of drug administrations.As the data (time required by brats to start a move in an open field)analyzed by 2 way ANOVA (repeated measured designing) the effect of cadmium acute and repeated administration ($F=78.10$,

df=1, 21, p<0.01) and the effect of repeated monitoring (F=41.68, df=1,21, p<0.01) and the effect of interaction between Cadmium and repeated monitoring (F=66.39, df=1,21, p<0.01) were significant. Post hoc analysis by Newman keuls test showed that administration of Cadmium increase activity (latency time) on single and on weeklyadministration in rats as compared to saline administrated rats. Significant increase was found after 14th (p<0.05), 21st(p<0.01) and 28th day of cadmium administration. As compared to similarly administrated rats of 1st day of administration, latency time in cadmium administrated rats increased. Significant (p<0.01) increase was found after 14thand 28thof administration.

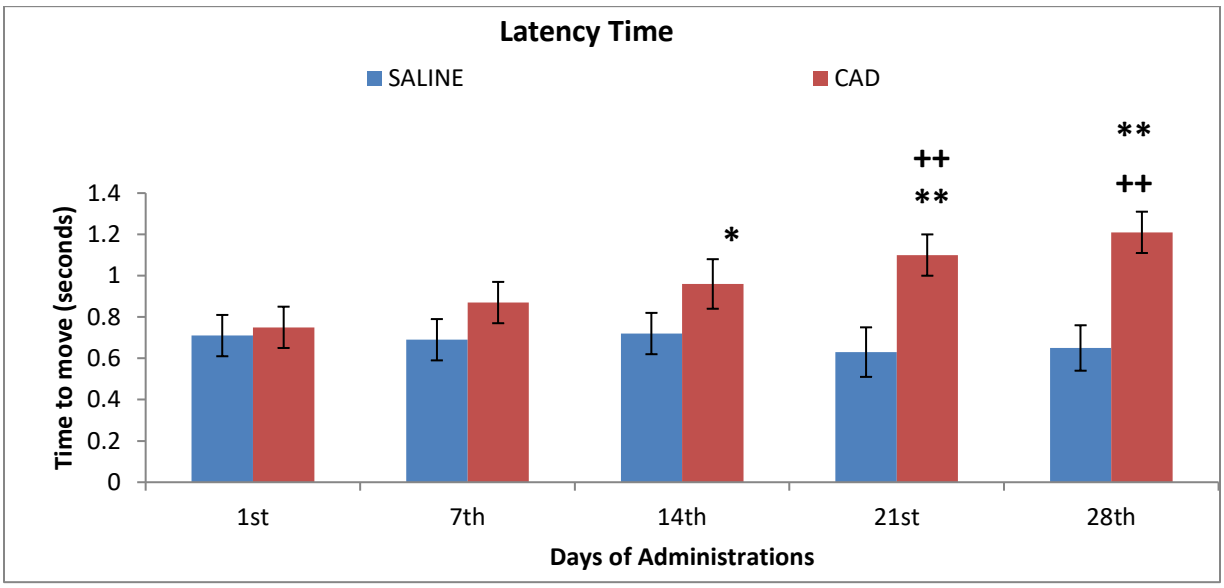

Figure 3: Effects of Cadmium on open field (latency) of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or Cadmium administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUM ADMINISTRATION ON OFT (SQUARE)OF RATS

Figure 4 shows the effect of Cadmium repeated administration on activity in novel environment (Number of square crossed) on rats for 28 days as they monitored after on next day of 1stdrug administration and then monitored weekly. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of repeated monitoring (F=67.49, df=1,21, p<0.01), the effect of Cadmiumadministration(F=89.25, df=1,21, p<0.01) and the effect of interaction between Cadmium and days (F=47.78, df=1,21. p<0.01) was found significant. Post hoc analysis by Newman keuls test showed that administration of Cadmium decreased activity in an open field (number of square crossed) as compared to saline administrated rats on acute and repeated administration. Significant (p<0.01) decreased was found after 7th, 14th, 21st and 28th day of administration. As compared to similarly administrated Cadmium administrated rats from 1st day of administration, number of square crossed decreased on in Cadmium administrated rats. Significant (p<0.01) decreased was found after 1st, 2nd, 3rd and 4th weeks of drug administrations.

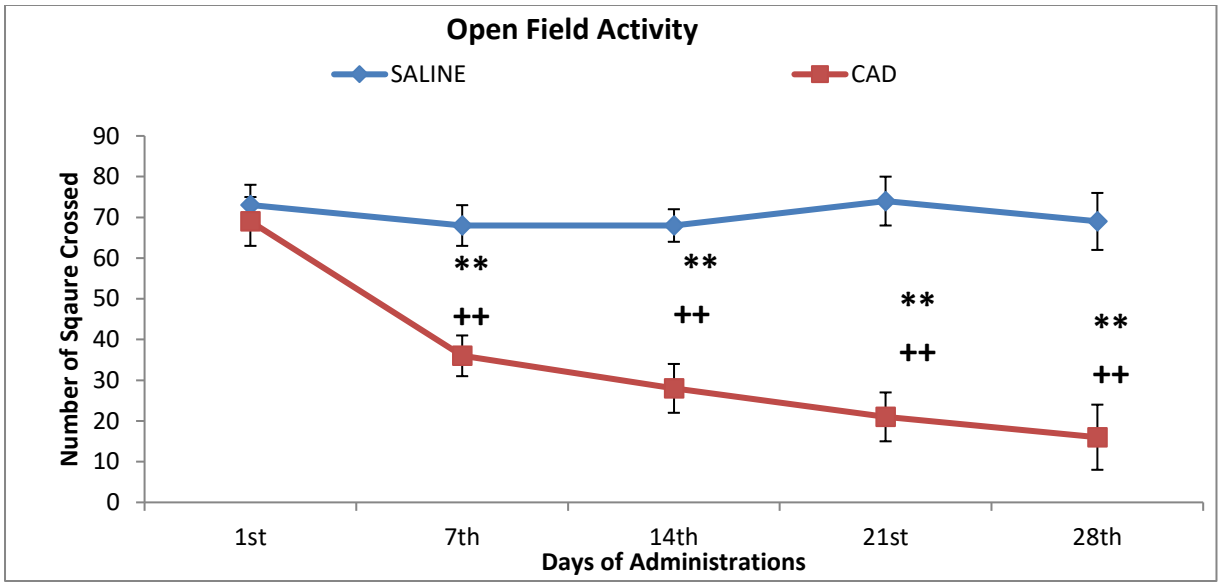

Figure4: Effects of Cadmium on open field (boxes crossed) of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administratedanimals; +p<0.05, ++p<0.01 from similarly saline or Cadmium administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUMADMINISTRATION ON EPMTEST OF RATS (ENTRIES)

Figure 5 shows the effect of Cadmium repeated administration on activity in EPM on rats for 28 days as they monitored after on next day of 1st drug administration and then monitored weekly. As the data (number of entries in open arm) analyzed by 2 way ANOVA (repeated measured designing) the effect of days (F=68.39, df=1, 21, p<0.01) and the effect of administration of cadmium (F=59.70, df=1, 21, p<0.01) were significant. Whereas, the effect of interaction between cadmiumadministration and repeated monitoring (F=4.23, df=1, 2) was not significant. Post hoc analysis by Newman keuls test showed that administration of Cadmium decreased activity (number of entries in an open arm) on single and repeated administration in rats as compared to saline administrated rats. Significant decreased was found after 7th(p<0.05) and (p<0.01) after 14th, 21st and 28thday of administration. As compared to similarly administrated rats of 1st day of administration, number of entries in open arm was decreased in cadmium administrated rats. Significant (p<0.01) decreased was found after 14th, 21st and 28th day of cadmium administration.

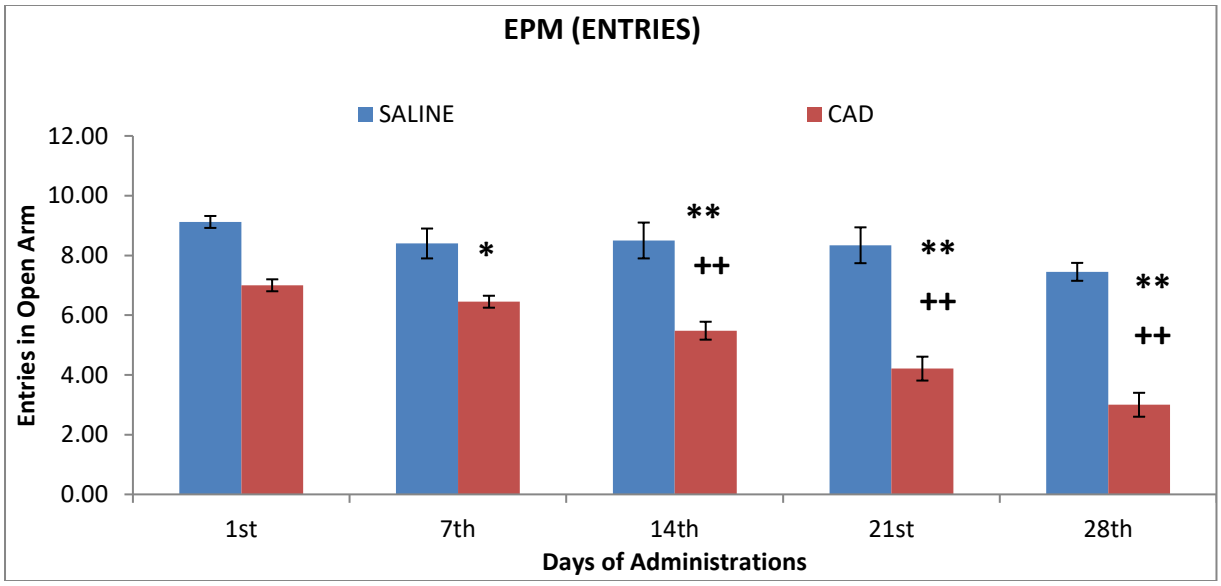

Figure5: Effects of Cadmium on EPM (Entries) of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administratedanimals; +p<0.05, ++p<0.01 from similarly saline or Cadmium administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUM ADMINISTRATIONON EPM TEST OF RATS (TIME)

Figure 6 shows the effect of Cadmium repeated administration on activity on EPM (time spend in an open arm) on rats for 28 days as they monitored after on next day of 1st day of drug administration and then after 1stn 2nd, 3rd and 4th weeks of drug administrations. . As the data (time spent by rats in an open arm of EPM) analyzed by 2 way ANOVA (repeated measured designing) the effect of days (F=79.34, df=1, 21, p<0.01), the effect of cadmium administration (F=71.44, df=1, 21, p<0.01) and the effect of interaction between Cadmium and days (F=51.89, df=1, 21, p<0.01) were found significant. Post hoc analysis by Newman keuls test showed that administration of Cadmium decreased activity (time required to move in open field) in EPM test in rats as compared to saline administrated rats. Significant (p<0.01) decreased was found after 14th, 21st and 28thday of administration. As compared to similarly administrated rats of 1st day of administration, activity (time spend in an open arm) was decreased in Cadmium administrated rats. Significant (p<0.01) decreased was found after2nd, 3rd and 4th weeks of administration.

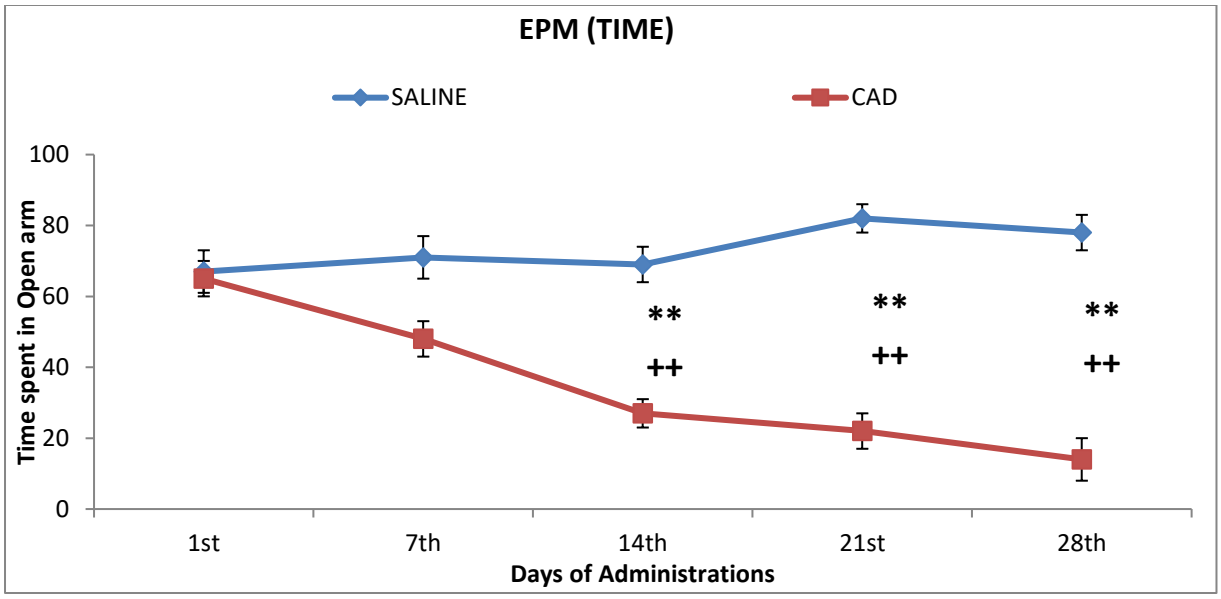

Figure6: Effects of Cadmium on EPM (Time) of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or Cadmiumadministrated animals of 1st day administration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUM ADMINISTRATION ON FST (IMMOBILITY TIME)

Figure 8 shows the effect of Cadmium repeated administration on activity in Force swim test (immobility time) on rats for 28 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 drug administration (F=68.45, df=1, 21, p<0.01) and the effect of repeated monitoring (F=41.55, df=1, 21, p<0.01) and the effect of interaction between cadmium and days (F=41.80, df=1, 21, p<0.01) were found significant. Post hoc analysis by Newman Keuls test showed that single and repeated administration of cadmium increasedimmobility time in rats as compared to saline administrated controls. Significant (p<0.01) increasein immobility time was found after 2nd, 3rd and 4th weeks of administration. As compared to similarly administrated rats of 1st day of administration, immobility time increase in cadmium repeatedly administrated rats. Significant (p<0.01) increase were found after 14th, 21st and 28thday of administration.

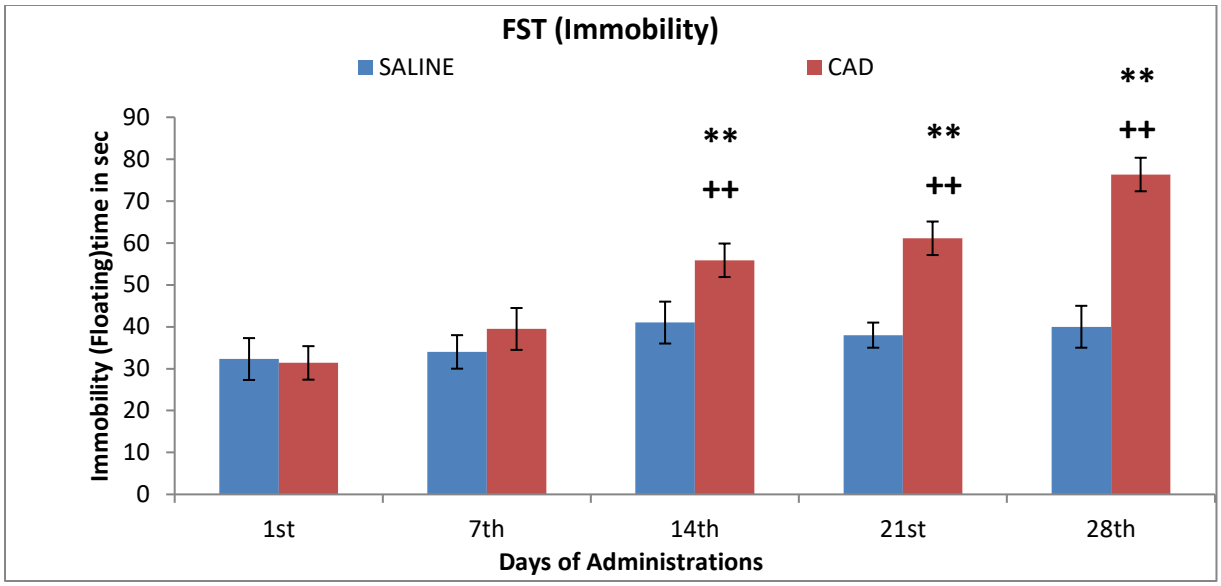

Figure 7: Effects of Cadmium on FST (Immobility Time) of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administratedanimals; +p<0.05, ++p<0.01 from similarly saline or Cadmium administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

EFFECTS OF CADMIUMADMINISTRATION ON FST (SWIMMING) OF RATS

Figure 8 shows the effect of Cadmium repeated administration on activity in force swim test (Swimming time) on rats for 28 days as they monitored after on next day of 1stdrug administration and then monitored weekly. As the data (swimming time) analyzed by 2 way ANOVA (repeated measured designing) the effect of cadmium administration (F=91.75, df=1, 21, p<0.01), the effect of days ofmonitoring (F=56.42, df=1,21, p<0.01)and the effect of interaction between cadmium and repeated monitoring (F=66.48, df=1,21;p<0.01) were found significant. Post hoc analysis by Newman Keuls test showed that administration of Cadmium decreased swimming time on acute and on repeated administration in rats as compared to saline administrated rats. Significant decreased was found after 14th (p<0.05), 21st (p<0.01) and 28th (p<0.01) day of cadmium administration. As compared to similarly administrated rats of 1st day of administration, swimming time decreased in cadmium administrated rats. Significant decreased was found after 2ndweek (p<0.05), after 3rd and 4thweeks (p<0.01) of cadmium administration.

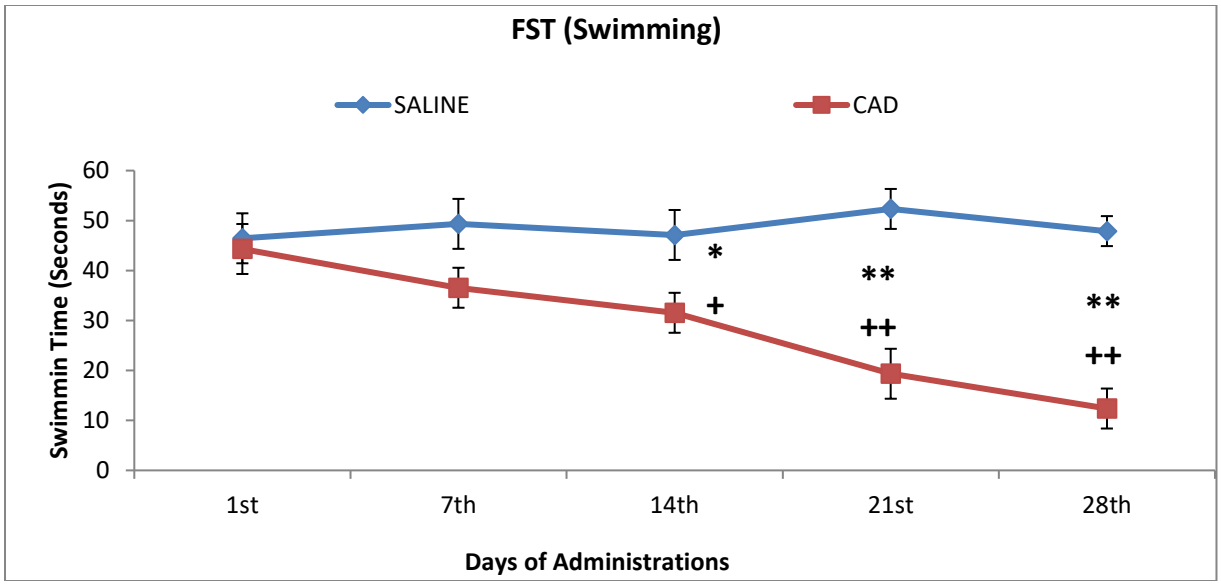

Figure 8: Effects of Cadmium on FST (Swimming) of rats for 28 days. Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations.Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or Cadmium administrated animals of 1st day administration following two-way ANOVA (repeated measures design).

DISCUSSION

Neurodegenerative diseases (NDs) encompass a range of progressive and often incurable conditions which act the central nervous system (CNS), leading to neurodegeneration and eventuallyto neural cell death, which cause a broad spectrum of symptoms from motor dysfunctions to psychobehavioral manifestations such as ataxia and dementia (Gitler A.D *et al.,*2017). Neurodegeneration, a structural and/or functional loss of neurons in the CNS, is a commonpathognomonic finding of the brain regions reflecting impairment and dysfunction of the correspondingmotor, autonomic, and/or cognitive nervous systems (Geon *et al.,* 2015). The neurodegenerative lesions of postmortembrain specimens correlate well with structural and functional imaging studies. The regional patterns of the brain shrinkage may help identify affected domains and diagnose diseases by magnetic resonance imaging (MRI) and positron emission tomography (PET) (Shimizu *et al.,* 2018).The purpose of this study was to see how repeated administration of Cadmium affected behavioral paradigms in rats like growth rate, food intake, open field activity, the elevated plus maze test and FST model. The purpose of this study was to see if repeated administration of Cadmium causes behavioral and memory problems. Cadmium is considered to be a potent neurotoxin. Nutritional deficiencies can increase the risk of cadmium toxicity.Cd can increase the blood brain barrier (BBB) permeability.Exposure to Cd severely affects the function of the nervous system.Cd-induced injury is thought to be responsible for damaging brain micro vascular tissue, including the cerebral micro vessels.Cd-induced neurotoxicity might be caused by impaired neurogenesis, resulting in markedly reduced neuronal differentiation and axonogenesis, leading to neuronal cell death. Cd significantly increases apoptosis, inhibits proliferation, and impairs spontaneous neuronal differentiation.

In this study, it was discovered that repeated administration of Cadmium caused adecrease in the growth rate of rats when compared to a control group given normal saline. A decrease in food intake was also observed in the Cadmium-treated rats when compared to their control counterparts, and a significant increase in growth rate was observed after the 14th day of drug administration. Based on this finding, it can be concluded that repeated Cadmium administration over a period of a few weeks causes hypophagia.Open field activity,the test group was repeatedly given Cadmium and showed a reduction in latency time in relation to their locomotive impairment, whereas the control group was given normal saline and showed the opposite. After the 14th day, the decrease in latency time is also quite noticeable. The number of squares crossed by the Cadmium-treated rats, on the other hand, decreased significantly after the 14th day, indicating locomotive impairment and rigidity in the animal.Elevated plus maze, all animals given Cadmium showed a decrease in the number of entries in the open arm as well as the time spent in the open arm in the above-mentioned study; the significant decline occurred after the 14th day of drug administration.

This accumulationof Cd in the brain after Cd treatment, revealed by the study of Jyostnaand Sudhakar (2016), provoking morphological and biochemical modifications,especially in certain of CNS structures and then leading to possible neurobehavioralalterations such as affective and cognitive disorders (Castro De *et al.,* 1996; Wester and Valois 1981). It is alsowell known in the CNS that the Cd acts as catalysts for biochemical reactions,regulators of gene expression, second messengers in signaling pathways and cofactorsfor many vital enzymes, such pathways implicated in regulating physiological,pathological and behavioral functions. In this direction, Cd is a neurotoxicsubstance that generally inhibits the enzymes involved in the synthesis ofneurotransmitters such as serotonergic system, which is one of several systemsinvolved in the response to anxiety and depression (File S.E, *et al.,* 2000). This is based on the observationthat people with low serotonin (5 HT) levels are more prone to depression and anxiety (Kamel M.M. *et al.,* 2011). Indeed, several studies have shown that exposure to Cdproduces alterations in the serotonergic system, which may explain the anxiogenicand depressive effect of this metal observed in our study. A decrease inlevels of 5-HT, dopamine in all regions of the brain including the anterior brain(hippocampus and striatum) has been shown 24 h after exposure to Cd (Taweel Abu *et al.,* 2013; Lafuente A *et al.,* 2001). Decreased levels of 5-HT and 5-HIAA in the cortex and hippocampus inprogeny was also observed following an exposure to low Cd concentrations indrinking water during the lactation period (Andersson H *et al.,* 1997).

All of the above findings showed that acute and repeated administration of Cadmium (10 mg/ml/kg) causes impairment in rat models when compared with the control given normal saline. This behavioral decline could also be characterized by locomotor impairment and motor dysfunction, as shown in previous studies using Cadmium to induce Neurodegenerative diseases in rats.

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