

Perinatal Exposure to Cadmium Affects Neurobehavioural Development and Anxiety – Like Behaviour in Rat Offspring

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Abstract: Cadmium is a known industrial and environmental pollutant. The present study was conducted to assess the potential influence of maternal cadmium (Cd) exposure on postnatal development and neuromotor maturation in offspring rats. Moreover, locomotors activity and anxiety – like behavior was also monitored post weaning. Cadmium chloride in doses of 0 , 5, 50 mg / L was administered orally in drinking water to pregnant rats from the 7th day of pregnancy till weaning of these pups at 30 days of age . All the females were allowed to deliver and wean their offspring. The pups were evaluated for physical development and neuromotor maturation (Reflexes). Also, open- field activity and anxiety- like behavior in elevated plus maze (EPM) were determined at weaning age of young rats. The results revealed that, birth weight of pups exposed to high doses of Cd was decreased relative to controls. A delay in some developmental landmarks (incisor eruption, vagina opening, testes descent) due to maternal cadmium exposure was also noticed pups. Moreover, a delay in neuromotor development (neonatal reflexes) and poor motor coordination was recorded in CdCl₂ exposed neonates. Cadmium – exposed offspring showed hyperactivity in open field test presented by increased horizontal locomotion. Anxiogenic effect of cadmium was evidently observed during open –field and elevated plus maze tests. Our results strongly suggest that maternal exposure to CdCl₂ in high doses has detrimental effects on the physical maturation & reflexes of neonate rats as well as anxiety – like behavior.

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Introduction

Cadmium (Cd) is a widespread toxic environmental and industrial pollutant. It is listed by the U.S. Environmental Protection Agency as one of 126 priority pollutants. In human, the primary route of exposure is via contaminated drinking water, food supplies, or tobacco. Normally, the main source of exposure to toxic compounds during the neonatal and first part of the infancy period is breast milk. This period is characterized by rapid growth and development of the nervous, immune, and endocrine / reproductive systems which render the newborn more vulnerable than adults to harmful substances (Rice & Barone Jr, 2000). The embriotoxic action of cadmium has been observed both in human studies and in animal experiments. In animals, cadmium can be transported across the placenta and excreted via the milk. Consequently, fetuses and pups can be exposed to Cd during gestation and lactation (Antonio et al; 1998).As the central nervous system of newborn animals is very susceptible to cadmium, the developmental pattern of certain neurochemicals in developing rat after Cd exposure during gestation and lactation periods was studied to explore the possible mechanism of Cd – induced neurotoxicity in growing animals (Desi et al; 1998). Lack of systematic studies on the effects of pre- and postnatal cadmium exposure

on behavioural and functional outcomes prompted us to clarify the effects of cadmium chloride exposure during pregnancy and lactation on behavioural development & anxiety – like behavior. This will help, to find sensitive biomarkers that can be used to signal the early risk of cadmium intoxication.

2. Materials and methods:

2.1. Animals and housing:

Thirty six pregnant female Wistar rats were obtained from the Unit for Laboratory Animals at Faculty of Veterinary Medicine, Cairo University. They were maintained in plastic cages, with stainless steel wire lids (bedded with wood shavings), on a standard laboratory feed diet. Feed and water were offered ad libitum. Rats were housed at a controlled temperature of $21 \pm 1^{\circ}\text{C}$, 60 % humidity and under a 12-h-light: 12-h-dark schedule. All efforts were made to minimize the numbers of animals and their suffering in this study through following the guidelines released by Cairo University Policy on Animal Care and Use.

2.2. Administration of cadmium chloride:

Pregnant females were divided at random into three groups of 12 each and received cdcl₂ in crystalline form (Sigma Aldrich) at one of three

different concentrations; 0 (control), 5 mg /L (low dose) and 50 mg / L (high dose) (Waalkes *et al.*, 1999). Cadmium chloride was incorporated in drinking distilled water and administered to pregnant rats ad libitum from day 8 of gestation till termination of lactation and weaning of pups. The pups were exposed to cadmium during the suckling period via milk and post weaning via drinking water.

2.3. Physical testing of offspring:

Pregnant rats were allowed to deliver and wean their offspring. At birth all pups were weighed and again at the age of weaning (on day 30). The Pups were evaluated for physical maturation, the day of occurrence for pinna detachment, incisor eruption, eye opening, fur growth. Also, vagina opening and testes descent were monitored.

2.4. Sensorimotor reflexes (neuromotor maturation):

The functional and behavioural developmental parameters were measured and scored for all individual offspring during the lactation period (Tanaka, 2006) and were analyzed on score frequencies. The measured variables were as follows:

- * Righting reflex test: was conducted on postnatal days 4, 5 and 6. Pups were placed on their back on a horizontal board and were released. Time to return to the normal dorso-ventral position was measured.
- * Negative geotaxis test: was conducted on postnatal days 7, 8 and 9 in which the animals were placed on 30° inclined screen, and the time spent turning upward was recorded.
- **Cliff avoidance: was assessed on postnatal days 7, 8 and 9, by placing the animal on the edge of a bench, with nose and forepaws just over the edge. Time to move away from the edge of a bench was recorded.
- *Startle responses: when a loud clap of the hands occurs less than 10 cm away, the pup shows a whole body startles response.
- * Vibrissa reflexes: when a cotton swab is stroked across the rat's vibrissa (whiskers), it places its paw on the cotton swab.

Both startle response and vibrissa reflexes are scored as 0 (no response), 1 (a slight response), and 2 (a complete response) (Meer and Raber, 2005).

*Balance test: on day 19, the ability to balance and move along the rim of a 2-liter beaker was tested, as described by Smart and Dobbing (1971). Percent of animals that fell from the rim was calculated and compared between groups.

2.5. Post- weaning behavioural tests:

At 30 days of pup's age, behavioural tests were performed in the first half of light phase of the light/dark cycle. All behaviours were scored by a

single trained observer unfamiliar with treated animals. Hand operated counters and stop watches were used to score animals' behaviour.

2.5.1. Open field behavior test:

The open field test provides simultaneous measures of locomotion, and anxiety (Kelly, 1993; Millan, 2003). The open field used was a square wooden arena measured (90 x 90 x 25cm). The wood of the apparatus is covered with a plastic laminate (formica), which prevents absorption of fluids (urine of rats). The floor was divided by black lines into 36 small squares (15 x 15cm). The open field maze was cleaned between each rat using 70% ethyl alcohol to avoid odor cues. The rats were carried to the test room in their home cages and tested once at a time for 5 minutes each. Rats were handled by the base of their tails at all times. Rats were taken from their home cages and placed randomly into one of the four corners of the open field facing the centre. The behavioural scores measured in this experiment included total numbers of line crossings (number of squares), rearing against the wall, and fecal boli as well as the time spent freezing (no movement) was quantified.

2.5.2. Elevated plus maze test:

The elevated plus-maze was used for testing of anxiety and emotionality. The degree of avoidance of the open arms of the maze has been considered as a measure of strength of fear drive (Trullas and Skolnick, 1993). The apparatus consists of 4 crossed arms, two open arms (50 x 10 x 30 cm) and two closed arms (50 x 10 x 30 cm). The maze was elevated 65 cm above the floor. The rat was placed in the centre of the maze and the number of entries in open and closed arms, respectively, as well as the time the animal spent in the open and enclosed arms during a period of 5 min test session was recorded (Kierstin, 2003; Walf and Frye, 2007). After each trial the maze was wiped out with a cloth dipped in 70% ethyl alcohol and allowed to dry.

2.6. Statistical analysis

Statistical analyses were performed by using SPSS statistical software package (SPSS, 2006). Data are presented as means with their standard error. Normality and homogeneity of the data were confirmed before ANOVA, differences among the experimental groups were assessed by one-way ANOVA followed by Duncan's test.

3. Results:

3.1. Physical development:

Physical maturation of pups all over the study was shown in Table 1. Lower body weight at birth

was significantly seen in groups of pups exposed to high concentrations of CdCl₂ compared to those exposed to low doses and pups in control group. Where no differences were observed in body weight at weaning age between control and experimental pups. Developmental landmarks were evaluated for all pups by a two-way ANOVA. No significant differences on pinna detachment or on the number of days at eye opening or fur growth. Where, there was a differences between groups on the number of days at incisor eruption. Moreover, effect of Cd was observed in both males and females in sexual maturation (vagina opening in females and testes descent in males) with significant differences between groups.

3.2. Neuromotor and neurobehavioural maturation

The effect of cadmium on neurobehavioural development in rat pups was demonstrated in Table 2,3,4,5,6. The righting reflex differed between groups, where a delay in this physical characteristic occurred in the Cd treated group (P< 0.05). The negative geotaxis reflex showed delay in the high Cd group (P< 0.05) when compared to the control group. A significant delay (P< 0.05) in cliff avoidance reflex was observed also between groups exposed to cadmium, especially high doses, and the control group. Moreover, pups exposed to CdCl₂ showed delay in startle response as well as vibrissa reflex. Concerning Balance and coordination, a significant impairment in motor balance was noticed in rats

treated with cadmium (increased percent of animals that fell from the rim of beaker) (Table, 7).

3.3. Open field test:

The effect of cadmium treatment on parameters of open field test was illustrated in Table, 8. Rats under cadmium intoxication increased significantly the mean covered distance in the open field test when compared with the control group. An anxiogenic like effect was obtained in cadmium-exposed rats when compared to their counterparts in controls. Cadmium -treated individuals presented a significant increase of rearing in peripheral area of the test. Also, administration of CdCl₂ to rats produced an anxiogenic profile of behavioural changes as indicated by increased time spent freezing. Moreover, a marked significant increase in fecal boli was also observed in rats following cadmium treatment when compared to animals belonging to control group.

3.4. Elevated plus maze test (EPM):

The effect of cadmium on measurement of elevated plus maze was demonstrated in Table, 9. Animals under cadmium effects significantly diminished the numbers of entries in the open arms of the maze, accompanied with significant increase of this measure in the closed arms. Regarding time spent in the open arms, cadmium was significantly successful in endorsing an aversive dose-related effect since the shortest time spent in open arm was recorded with high cadmium group.

Table (1) : Effect of CdCl₂ on physical maturation of the offspring of prenatally exposed rats.

Parameters / groups	Control	Low	High
-Birth weight (gm).	6.57±0.37 ^{ab}	6.17±0.46 ^{ab}	3.72±0.46 ^c
-Weight at weaning (gm).	28.37±1.30 ^{abc}	29.56±1.76 ^{abc}	31.90±2.1 ^{abc}
-No. of days at pinna detachment.	2.8±0.40 ^{abc}	2.75±0.43 ^{abc}	3.00±0.00 ^{abc}
-No. of days at incisor eruption.	3.00±0.00 ^{ab}	3.75±0.43 ^{ab}	2.43±0.50 ^c
-No. of days at fur growth.	7.2±0.40 ^{abc}	6.88±0.60 ^{abc}	7.00±0.58 ^{abc}
-No. of days at eye opening.	14.6±0.40 ^{abc}	14.8±0.50 ^{abc}	15.8±0.64 ^{abc}
-No. of days at testes descent.	22.9±0.60 ^{ab}	23.8±1.10 ^{ab}	26.8±2.50 ^c
-No. of days at vagina opening.	30.9±4.10 ^{ab}	32.5±3.60 ^{ab}	42.9±5.40 ^c

a-c values within row with unlike superscripts differ significantly (p < 0.05) ; according to ANOVA . Values represent mean ± SEM.

Table (2): Effect of CdCl₂ on the righting reflex of neonates .

Day/groups	Control	Low	High
4day	3.83±0.76 ^a	2.41±0.21 ^{bc}	2.45±0.25 ^{bc}
5day	1.35±0.09 ^{ab}	1.60±0.15 ^{ab}	2.34±0.37 ^c
6day	1.38±0.14 ^{ab}	1.25±0.07 ^{ab}	2.39±0.06 ^c

a-c values within row with unlike superscripts differ significantly (p < 0.05) ; according to ANOVA . Values represent mean ± SEM.

Table (3) : Effect of CdCl₂ on the negative geotaxis of neonates.

Day/groups	Control	Low	High
7day	9.03±0.90 ^{ab}	10.73±0.88 ^{ab}	15.18±1.57 ^c
8day	10.03±1.46 ^{ab}	9.79±0.76 ^{ab}	13.86±2.04 ^c
9day	10.07±2.03 ^{ab}	9.47±98 ^{ab}	13.70±1.01 ^c

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SEM.

Table (4) : Effect of CdCl₂ on the cliff avoidance of neonates .

Day/groups	Control	Low	High
7day	4.76±0.60 ^{ab}	4.64±0.34 ^{ab}	6.94±0.65 ^c
8day	2.74±0.38 ^{ab}	2.95±0.23 ^{ab}	6.14±0.86 ^c
9day	2.71±0.41 ^{ab}	3.77±0.43 ^{ab}	6.71±1.47 ^c

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SEM.

Table (5) : Effect of CdCl₂ on the startle response of neonates (% of neonates).

Scores	Control(n=28)	Low (n=49)	High (n= 28)
0 (no response)	00.00(0)	2.04(1)	00.00(0)
1 (slight response)	17.85 ^a (5)	51.02 ^{bc} (25)	60.71 ^{bc} (17)
2 (complete response)	82.14 ^a (23)	46.94 ^{bc} (23)	39.29 ^{bc} (11)

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SEM.

Table (6) : Effect of CdCl₂ on the vibrissa reflexes of neonates (% of neonates).

Scores	Control(n=26)	Low (n=49)	High (n= 30)
0 (no response)	15.38 ^{abc} (4)	14.29 ^{abc} (7)	13.33 ^{abc} (4)
1 (slight response)	38.46 ^{ab} (10)	26.53 ^{ab} (13)	56.67 ^c (17)
2 (complete response)	46.15 ^{ab} (12)	59.18 ^{ab} (29)	30.00 ^c (9)

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SE

Table (7) : Effect of CdCl₂ on balance of neonates (% of neonates).

Items / groups	Control(n=41)	Low(n=18)	High(n=18)
No. of animals that fell From the rim.	9.76 ^{ab} (4)	11.11 ^{ab} (2)	44.44 ^c (8)

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SEM.

Table (8): Effect of Cadmium on the behavior of rats in the open field test.

Items / groups	Control	Low	High
No.of squares crossed	26.87±6.71 ^{ab}	28.29±6.95 ^{ab}	58.00±7.21 ^c
No.of rears in the periphery.	05.13±1.03 ^{ab}	04.07±1.06 ^{ab}	11.00 ±1.10 ^c
Freezing (immobility time).(s).	1.00 ±0.85 ^a	3.20 ±2.48 ^{bc}	4.60 ±2.48 ^{bc}
No. of fecal boli.	2.61 ±0.50 ^{ab}	2.47 ±0.55 ^{ab}	4.00 ±0.64 ^c

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SEM.

Table (9): Effect of Cadmium on the behavior of rats during the elevated plus maze test.

Items / groups	Control	Low	High
No.of entries(open arm)	11.00±3.13 ^a	5.15±3.01 ^{bc}	3.20±2.80 ^{bc}
Time spent (open arm)(s)	123.62±15.26 ^{ab}	117.15±16.39 ^{ab}	64.25±17.06 ^c
No.of entries(closed arm)	3.62±0.57 ^{abc}	5.92±0.57 ^{abc}	6.52±0.46 ^{abc}
Time spent (closed arm)(s)	60.46±12.20 ^a	108.77±12.20 ^{bc}	146.85±9.30 ^{bc}

a-c values within row with unlike superscripts differ significantly ($p < 0.05$) ; according to ANOVA .
Values represent mean ± SEM.

4. Discussion:

Studies in rodents have shown that, exposure to certain metal levels during gestation can cause maternal and developmental toxicity (Domingo et al; 2004). Our study, observed marked decline in birth weight of pups exposed to high doses of cadmium chloride in perinatal period. A significant retardation of intrauterine development manifested by lower body weight was reported in former study with female rats orally treated with CdCl₂ (Barański, 1984). World Health Organization (WHO) (2001) confirmed that birth weights of newborn infants may be lower following maternal cadmium exposure. Unlike birth weights, our results reported no differences in body weight at weaning between control and experimental groups. Similar results derived from other studies with cadmium treated animals (Antonio et al., 2002). Also, Kierstin (2003) recorded no significant differences in body weights between the groups of pups prenatally exposed to cadmium.

Regarding physical maturation, the results showed delay in incisor eruption of pups exposed prenatally to high concentration of cadmium. Moreover, the data reported here revealed a negative effect of high concentration of CdCl₂ on sexual maturation in terms of increased number of days at testes descent and vagina opening. In addition, no significant differences on pinna detachment or on the number of days at eye opening or fur growth were observed.

The results of the present work revealed that prenatal cadmium exposure produces a delay in neuromotor and neurobehavioural development of neonates (neonatal reflexes) in terms of righting reflex, negative geotaxis, cliff avoidance, startle responses and vibrissa reflex. In agreement with our results, Environment Agency (EA) (2009) reported that offspring from female rats exposed to 0.02-0.04 mg kg⁻¹ bw day⁻¹ prior to and during gestation showed impaired reflexes.

Regarding balance and coordination, impairment of rat's motor balance after ingestion of CdCl₂ has been proven in the present study. Cadmium treated group exhibited the highest number of animals that fell from the rim of beaker. These results are consistent with former studies in rats (Ali et al., 1990; Hans, 2006; Ka-oud et al., 2010). Further support for impaired motor balance derived from increased symptoms of fatigue and disturbance of sensory & motor function (Murphy, 1997).

The current reduced birth weights & delay of some parameters of physical maturation and reflexes of neonates exposed prenatally and postnatal to high doses of cadmium might be explained on the basis of CdCl₂ -induced adverse effects on serotonin, controlling body weight and maturation of reflex

responses during the perinatal period in rats. Experimental evidence indicates that serotonin can influence embryogenesis and growth (Palén et al., 1979; Whitaker-Azmitia 1991). Furthermore, serotonin seems to play a role in regulating the development of the mammalian brain through actions on the serotonergic neurons (Whitaker-Azmitia & Azmitia 1986; Shemer et al., 1991; Whitaker-Azmitia 1991). Also, Aghajanian and Marek (1997) reported the serotonin as a neurotransmitter has modulating effects on the neural excitability. Further support derived from earlier rat study for Teresa Cristina et al., (2008), where increased brain serotonin in young animals modulates their neuro- behavioural responses and growth.

The serotonergic system was found to be the most susceptible transmitter system in developing brain after cadmium exposure. Serotonin (5-HT) and its metabolite 5- hydroxyindoleacetic acid in cerebral cortex were reduced in pups exposed during suckling or during both the suckling and post weaning period (Kierstin, 2003). Confirmatory results derived from other study for Leret et al., (2003), where maternal co-exposure to lead and cadmium produced alterations in serotonergic & dopaminergic systems of hippocampus.

The results showed that exposure to cadmium during the gestational & lactation period delayed the birth weight of young and the development of early behavior expression. Morphological or functional alterations produced during the period of fast brain development, indicating the participation of the serotonergic mechanisms in these events. These findings together with previously mentioned observations go hand in hand with and further confirm the serotonin importance for maturation of most reflex responses during the prenatal & postnatal period in rats.

As the Environment Agency (EA) (2009) reported that cadmium can be fetotoxic, the most sensitive indicator appearing to be neurobehavioural development, with effects being seen on locomotor activity at around 0.2 – 0.4 mg cadmium kg⁻¹ bw day⁻¹. Open field activity monitoring provides a non-invasive method for an accurate and comprehensive assessment of the motor activities of rats. The number of line crossing is usually used as a measure of locomotor activity, with high frequencies of this behaviour indicating increased locomotion activities (Eisenhaver and Murphy, 1998). In this study and as a trial to dissociate between “general activity” and “exploration”, ambulation was only related to horizontal locomotion (amount of distance traveled) than vertical activity (rearing) which is more sensitive to anxiety state of the individual (Lapin et al., 1995; Brown et al., 1999). In the present work, increased

locomotor activity was noted in cadmium – exposed rats in the open field test .Animal studies with cadmium have shown that exposure leads to motor hyperactivity (Rastogi et al , 1977, **Wong and Klaassen** 1982). Also, in accordance with our data, Antonio et al., (2002) have observed alterations in motor activity in rats intoxicated with cadmium. Data reported in our previous article (Ka-oud et al., 2010), confirmed this justification, where cadmium-treated rats exhibited higher levels of activity upon exposure to open field test as revealed in enhanced line crossing. In contrast to our results Desi et al .,(1998) demonstrated that cadmium treatment during prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical exploratory activity and a significantly lower exploration frequency of the open-field centre. This discrepancy in results might be attributable to the different inoculated doses. Here, the enhancing effect of cadmium on locomotor activity might be explainable on the basis of endogenous levels of norepinephrine, dopamine and serotonin in various brain regions of cadmium-treated rats. Repeated daily intraperitoneal (i.p.) administrations of cadmium (CdCl₂, 1 mg/kg per day for 5 days) increased striatal dopamine (DA) release in 13-day-old rats (Elsa et al., 1998).

Anxiety in rats can be measured by behavioral reactivity to non-social or social stressors (Kim et al., 2004). These behaviors were compared by performing the open-field and elevated plus maze tests (non-social). With regard to the present study, it is important to note that most of the behavioural models cited above have mainly been used in the studies on the neurobiological mechanisms implicated in the production of fear and anxiety elicited in animals exposed to aversive situations (Rodgers and Dalvi, 1997; Menard and Treit, 1999).

The present work revealed that cadmium chloride caused a significant increase in the anxiety levels of rats in both of anxiety models used. Few researches have implemented open field test to investigate CdCl₂ influence on anxiety levels in rats .Measures of anxiety in the open field test; number of rearing against the wall, freezing (immobility) as well as number of fecal boli, all parameters were greatly influenced by high dose of cadmium. Increased rearing behavior in the periphery has been proved to reflect higher levels of anxiety in rats (Anderson and Hughes, 2008). Supporting evidence for highly anxious rats in the current study derived from increased freezing time (immobility).Freezing has been validated as indicator of anxiety (Kalueff & Tuohimaa, 2004). Where fecal boli were shown to be a sensitive measure for anxiety state of animals

(Singer et al., 2005), toxicity with cadmium revealed enhance in defecation.

Also, data derived from elevated plus maze further affirmed the previously observed effect of cadmium on anxiety-related behaviours during open field test. Currently, data of elevated plus maze test revealed that cadmium treated animals exhibited low number of visits for open arms in EPM. Moreover, the less time was observed with high dose-administered rats indicating that they avoid this aversive region of the maze as reported in other studies (Bhattacharya et al., 1995; Schulteis et al., 1998). Therefore, time elapsed in the open arms might be considered as the more sensitive index for anxiety than number of visits. Our results are in line with data of (Bull, 2010) who stated that sub chronic oral exposure to cadmium can cause anxiety and alterations in the biochemical activity of the brain in laboratory animals .Also, Leret *et al.* (2003) recorded that, the intoxicated rats with cadmium and lead acetate, showed an increase on indices of anxiety on the elevated plus maze. These long –term changes in anxiety – like behavior can be related to dopaminergic and serotonergic alterations detected in hippocampus. Where serotonin system is important in the pathophysiology of psychiatric disorders including mood and anxiety, healthy levels of serotonin is essential to promote balanced mood (Millan, 2003; Dayan and Huys, 2008). The hippocampal serotonergic alterations have been reported to play an important role in control of anxiety, depression and other mood disorders (File et al., 1996, 2000). Thus, the results indicate that neurochemical and neurobehavioural effects during development may be a more sensitive target for cadmium toxicity in animals models. Taken together, this study suggested that cadmium intoxication in gestational and lactation stage has negative potential effect on neuromotor maturation and behavioural development of neonates. Since maternal cadmium ingestion constitutes a great threat to progeny, caution should be exercised when products containing cadmium are administered to nursing mothers.

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