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Behavioral Toxicity of Cadmium in Normal and Protein Malnourished Rats (Two-Generation Study)

Syed Saleem Husain*

Division of Medical Chemistry, Faculty of Applied Medical Sciences, Jazan University, Jazan, KSA

Abstract

Assessments of behavioral toxicity of cadmium (Cd, 50 ppm, through drinking water for 120 days) were carried out in growing male rats, maintained on diets containing 21% and 8% protein. The effects of chronic exposure to cadmium toxicity were studied both in Fo and F1 generations.

The low protein diet (8%) caused a significant reduction in the litter size, a delay in the physical developmental landmarks like less body weight and eye opening, and also caused marked delay in the development of sensory–motor reflexes like visual placing, cliff aversion, in the F1 offspring. The viability and lactation indices were not significantly affected.

Cadmium exposure resulted in significant growth retardation in both the dietary groups of the Fo–generation rats during the growing, gestation and lactation periods. A significant delay in the development of the criterion response in the ascending wire mesh test was observed in the pups of cadmium exposed malnourished dams only whereas the development of beam balancing ability was significantly delayed in the pups of cadmium exposed dams of both the diet groups but the effect was more marked in the protein malnourished groups.

The data indicate the enhanced vulnerability of protein malnourished animals to the behavioral aberrations caused by Cd toxicity.

Keywords: Protein malnutrition; Cadmium; Behavioral aberrations; Albino rat

Introduction

The wide–spread environmental occurrence of Cd increases the risk of exposure to it, in organisms during their vulnerable stages of development. Further, the toxic effects of environmental insults, sustained during the embryonic development, are likely to be revealed during the immediate postnatal and even in the late adult life. Ali et al. [1] have investigated the developmental and behavioral toxicity of gestational exposure to low levels of cadmium (Cd 4.2 and 8.4µg/ml, in drinking water) in rats. Significant decreases in birth weight and growth rate were observed in the 8.4 µg/Cd/ml group. The metal exposure had no effect on the ontogeny of Physical landmarks, surface and air righting reflexes and visual placing, but a significant hyperactivity and delay in the development of Cliff aversion and swimming behavior were observed in the neonatal pups of either treatment group. Marked decreases in the locomotor activity and shuttle box performance were evident at 60 days but not at 90 days of postnatal life.

M. Mohamed Ali et al. [2], gave cadmium (Cd, 100 ppm, through drinking water for 60 days) to growing male rats, maintained on diets containing 21, 8 and 5% protein. Cd exposure in the 21% protein diet fed rats resulted in decreased body weight and growth, spontaneous locomotor activity and learning ability. The response latency in the learning situation was enhanced significantly. The decreases in the locomotor activity and learning ability were more marked in the 5% protein diet fed animals. The increase in the response latency was, however, more marked in the 8% protein diet fed group. The study indicates the enhanced vulnerability of protein malnourished animals to the behavioral deficits induced by Cd.

Assessment of the effects of cadmium on locomotor activity and learning performance in growing rats has been reported [3]. The same authors in another study fed low levels of cadmium (4.2 and 8.4 µg/ml) in drinking water to rats and concluded with the data that cadmium exposure during the critical periods of development might result in developmental and behavioral deficits with long term implications on adult behavior.

Alteration in antioxidant defense system in the rat testes was found with Cd exposure [4]. Studies showed toxic nephropathy might be detectable in an early stage by assay of the enzymes in urine. Cd exposure leads to decrease in glutamate, aspartate, glutamine, GABA and taurine content of rat striatum [5]. Cadmium chloride (CdCl2), administered during gestation period on female wistar rats resulted in decrease in body weight gain and induced hepatotoxicity [6].

Another major factor which has to be taken into consideration in assessing the toxicity of environmental pollutants is the increased vulnerability of the young and immature organisms to the toxic effects of these toxicants. Clinical and experimental studies have shown that children are more susceptible to the toxic effects of heavy metals like Pb and Hg [7,8] and the toxicity of Pb, Mn, Hg, polychlorinated biphenyls and diazepam are more pronounced in the prenatal and neonatal phases than in adulthood [1,9-13]. Hence, it is essential to assess the toxicity of environmental pollutants in the adult as well as the young developing organisms. Human and animal studies have shown that protein malnutrition causes reduction in the brain development

***Corresponding author:** Syed Saleem Husain, Assistant Professor, Division of Medical Chemistry, Faculty of Applied Medical Sciences, Jazan University, Jazan, KSA, Tel: 0173235109 or 0503655173; E-mail: drsaleemsaim@gmail.com

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lowered intelligence and reduction in the learning ability [14-17]. Kwashiorkor and the protein deficient diet that preceded it have been found to cause a poor mental performance in children [18].

Many previous investigations have revealed the behavioral effects of Cd exposure in neonatal and adult rats [19-23].

In the present research, effects of cadmium toxicity were studied in Fo as well as F1 generation of albino rats. These studies were of chronic type and a low dose level of cadmium exposure was maintained through drinking water. Hence, the absorption of cadmium was through gastro intestinal tract (GIT).

The studies were conducted along the following lines

Long term studies (120 days) were conducted in growing rats exposed to cadmium (50 ppm. through drinking water). The effects were assessed in normal (21% protein) and protein–deficient (8% protein) diet fed rats. Other than hepatic and renal toxicity [24], prominent behavioral aberrations are reported in the present paper.

Materials and Methods

All chemicals/ reagents used for these experiments were of high quality research grade. All major chemicals were purchased from Sigma Chemical Co. (USA) and olive oil was purchased from the local supplier. Behavioral parameters were performed using the following:

Experimental animals

160 weaned male rats of a wistar–derived strain, about 25- 35gm, were randomly allocated into four groups of 40 rats in each: Group (I) 21% protein diet + drinking water (control), (II) 21% protein diet + drinking water (Cd, 50 ppm), (III) 8% protein diet + drinking water (control) and (IV) 8% protein diet + drinking water (Cd, 50 ppm).

The animals were fed with standard Wetherholtz diet, had free access to water under well ventilated condition of 12h light cycle. The animals were adapted to laboratory condition for 7 days prior to the experiments. Investigations using experimental animals were conducted in accordance to the Organization for Economic Cooperation and Development guidelines no. 407 (OECD, Paris, 1993). The studies were performed with the approval of Institutional Animal ethics committee (IAEC).

Mating and parturition

After 120 days, batches of male and female rats were cohabited and an F1 generation was raised, in which several developmental parameters (apart from some parturition data viz. litter size, litter weight and still birth) were conducted. The list of development parameters is as follows: viability and lactation indices, surface righting, air righting, swimming pattern, cliff aversion, ascending wire mesh, visual placing, and beam balance.

Meanwhile physical landmarks were also looked for their onset. They included: eye opening, ear opening, molar eruption and fur growth.

Pre-weaning evaluation

The pups were weighed daily. The various developmental parameters were monitored using different batches of 8–10 pups, drawn at random by litter mate control, by the observer blind to the treatment groups. Care was exercised for minimal handing of the pups.

Viability and lactation indices

These indices were calculated as follows:

$$\text{Viability Index} = \frac{\text{No. of pups alive at 4 days}}{\text{No. of pups born alive}} \times 100$$

$$\text{Viability Index} = \frac{\text{No. of pups alive at 21 days}}{\text{No. of pups alive at 4 days}} \times 100$$

Morphological development: From birth the pups were observed for the appearance of fur onset, eye opening, pinna detachment and incisor eruption.

(a) Fur onset: Each pup was held in the air against light and screened closely for the appearance of the fine downing hair [25].

(b) Eye opening: The criteria for eye opening was the appearance of a perceptible break in the supra-ocular membrane and the age at which both the eyes opened were recorded [26].

(c) Pinna detachment: The pups were observed daily until both pinnas on all test pups were detached [27].

(d) Incisor eruption: The pups were observed daily until both upper and lower incisors had erupted in all test pups [27].

Surface righting: It tests motor and vestibular integration. This test was initiated on postnatal day 3. The pups were placed on their back held momentarily and then released. Criterion was achieved when the rat was able to attain a fully prone position within 2 sec. three successive times [28].

Air righting: It tests motor and vestibular integration. From day 10 of age until appearance of criterion response a neuromuscular test using a gravity stimulus was administered to the pups [29]. The pups were dropped from a height of 30 cm above some wood shavings. Each pup was given three trials per day and criterion response was two or three trials in which the rat righted in mid–air and landed on all four feet. The age at first criterion was recorded for each pup.

Visual placing: It tests visual activity. The rat was lowered head–first towards a horizontal wire (3 mm diameter), placed 30 cm above the table top, care being taken that vibrissae did not touch the wire. Criterion was achieved when the rat extended the head and forelimbs towards the wire in two successive trials. The visual placing test was initiated on day 10 of postnatal life [21].

Cliff aversion: This is a test for sensory–motor coordination. From postnatal day 3 each pup was placed on a wooden platform elevated 20 cm above a table top. The animal was positioned in such a way that the forepaws and the snout protruded beyond the edge of the platform. The latency required for retraction of the head completely behind the edge of the platform was recorded daily. A criterion of a retraction response < 20 sec was used. If the animal was not successful within 60 sec, the trial was terminated. If the animal fell down, it was given a second attempt. And, if it fell again, a latency of 60 seconds was recorded [30].

Swimming behavior: It tests the animal's ability to coordinate and integrate a complex series of reflex responses. The development of the swimming behavior was assessed from day 3 of age. The pups were placed individually in a tank (30% 30 cm) with the water temperature maintained at 240°C. The animals were given a maximum of 15 sec in the water and were then removed to a warm, dry towel to dry. The swimming pattern was ascertained by judging the score based upon the direction and the head angle [31].

(i)	Direction –	(a)	Straight–3
		(b)	Circling–2
		(c)	Floating–1
		(d)	Sank–0
(ii)	ead angle –	(a)	Ears out of water –4
		(b)	Ears half out–3
		(c)	Nose and top of head–2
		(d)	out of water
			Unable to hold head–1
			above water

Ascending wire mesh: A wire mesh was stood inclined making 450 angles with the platform. Each pup was given three trials to ascend the wire mesh. Any one successful trial (out of the three trials) was taken as the criterion response for the pup and the day recorded [32].

Balance beam test: The pups were suspended by the tail and placed lengthwise on a wooden dowel 19 mm (3/4 inch) in diameter, fixed 30 cm above a foam pad. This diameter of the dowel was selected based upon pilot data showing larger or smaller diameters to be less sensitive. During a 30 sec trial, the examiner recorded the time the animal balanced on the dowel and the following scores assigned:

Score		Description
0		Animal is unable to maintain grip or balance on wooden beam.
1		Animal remains balanced on beam for 10 sec.
2		Animal remains balanced on beam for 11-20sec.
3		Animal remains balanced on beam for 21-30 sec.

The day of achieving the criterion score of 3 in each group was recorded [33].

Day of diet ingestion: The day the pups started nibbling the diet was recorded as the day of diet ingestion.

Statistical analysis

All the biochemical, hematological and development parameters were analyzed by the One–Way ANOVA.

The data on body weight, diet and water consumption were analyzed by the Two–Way ANOVA (repeated measures). Separate analyses were done on the data for each parameter obtained at each time interval. The tests were applied after ascertaining the homogeneity of variance and normality assumptions of the data. If the overall F ratio was found to be computation of the LSD statistic, post-hoc comparisons were made by computation of the LSD statistic. The significance levels were ascertained at $P < 0.05$, 0.01 and 0.001.

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Results

Growth and development: Cd exposure resulted in significant retardation in body weight growth in both the normal and protein malnourished animals. This growth retardation was evident from 9th week onwards in the normal protein diet fed animals but in the malnourished rats significant loss in body weight was observed only from the 14th week of exposure (Figure 1).

Consummatory behavior: (a) - Diet consumption

All the groups were pair–fed. Cd exposure in either diet group had no significant effect on diet consumption. The diet consumption in the Fo–rats during the different stages of the experiment is as under:

Fo–growing period

Days	30	60	90	120
Diet consumption (g/rat/day)	8.2–11.3	11–14	14–17	17.5–19.5

Fo– gestational period: 16.3–34.2

(iii)Fo – lactation period: 20.64–34.5

(b) Water consumption and Cd intake range

The daily water consumption in protein malnourished groups were significantly lower than that in the normal protein diet fed animals during the gestation and lactation periods but it was not significantly affected in the Cd–exposed animals of both the dietary groups, compared to their respective controls. The water consumption in the Cd–exposed groups over the experimental period is tabulated. The Cd intake in the malnourished animals calculated on body weight basis, did not differ significantly from that of the normal protein diet fed rats(Table 1).

Body weight growth: Cd exposure resulted in significant growth retardation in both the dietary group of the Fo– and F1 generation rats, during the growing, gestation and lactation periods. This effect of Cd was more marked in the normal protein diet–fed animals than in the protein malnourished rats (Figure 1).

Parturition data: The dietary and Cd exposure schedules had no significant effect on the number of pregnancies, deliveries of still births. The litter size in the malnourished groups was significantly lower than that of the normal protein diet–fed animals but Cd exposure has no significant effect on the litter size in either dietary group. Low protein diet as such and Cd exposure (in normal protein diet group only) resulted in a significant decrease in the birth weights of the pups (Table 2).

Developmental toxicity (pre-weaning evaluation)

(i)- Viability and lactation indices:

The low protein diet as such and Cd exposure had no significant effect on the viability and lactation indices (Table 3).

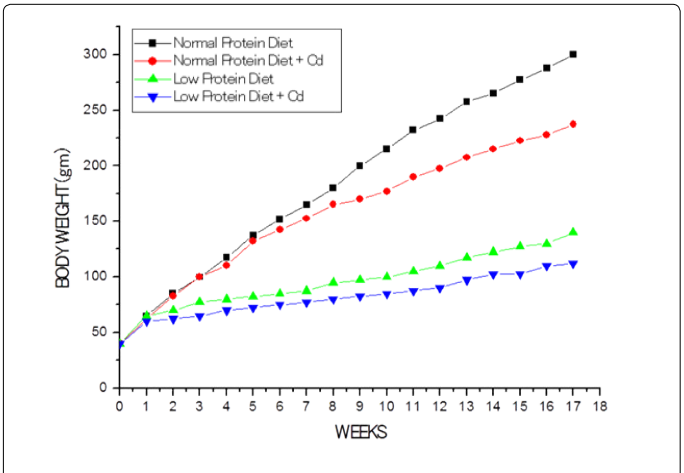

Figure 1 Developmental toxicity of cadmium in normal and protein malnourished rats

Stage of experiment		Normal protein diet group		Low protein diet group	
		Water consumption (ml/day/rat)	Cadmium intake (mg/kg/day)	Water consumption (ml/day/rat)	Cadmium intake (mg/kg/day)
i	Fo–growing period	9.8 – 20	3.36 – 5.58	5.3 – 15.0	3.52 – 5.84
ii	Fo–gestation period	24.9 – 41.1	5.08–6.73	15.74 – 25.68	5.83 – 7.15
iii	Fo–lactation period	28.3 – 46.52	5.57 – 8.02	17..64 – 26.77	6.21 – 7.92

Table 1: Water consumption and Cd intake range

Group	No. of deliveries / No. of +ve pregnancies	Total No. of stillbirths	Gestation litter Size	Birth weight of F1 pups
Normal protein diet	18 / 20	7	5.83 + 0.67	6.82 + 0.35
Normal protein diet	19 / 22	9	7.91 + 0.72	5.11 + 0.21 **a
+ Cd	NSa		NSa	
Low protein diet	16 / 18	11	6.17 + 0.79	5.62 + 031
Low protein diet	16 / 19	10	5.93 + 0.45	4.95 + 0.35
+ Cd	NSb		NSb	NSb

Table 2: Parturition data of normal and low protein diet fed Fo dams exposed to Cd 120 days prior to and during gestation
Values represent mean + SE of 16–19 litters
Statistical analysis by one–way ANOVA, followed by LSD comparison
a = Compared to normal diet protein control, b= Compared to low protein diet control
p ** =<0.01, N S = Non-significant

Group	Viability index	Lactation index	Day of			
			Fur onset	Pinna detachment	Eye opening	Incisor eruption
Normal protein diet (normal)	99.3 + 4.72	100	6.31 + 0.77	3.25 + 0.20	13.79 + 0.41	9.71 + 0.78
Normal protein diet + Cd	91.23 + 5.31	99.75 + 0.90	6.75 + 0.91 NSa	3.32 + 0.26 NSa	14.96 + 0.65 Nsa	10.24 + 1.31 NSa
Low protein diet (control)	98.61 + 1.34	100	7.72 + 1.19	3.82 + 0.32	13.89 + 0.37	10.15 + 0.74
Low protein diet + Cd	95.17 + 2.44	93.98 + 4.34	7.35 + 1.62 NSb	3.64 + 0.21 NSb	15.66 + 0.46 *b	10.43 + 0.61 NSb

Table 3: Effect of concurrent low protein diet and Cd exposure on certain developmental indices in F1–pups
Values represent the mean + SE of 8–10 pups (litter mate)/litters
Statistical evaluation by one–way ANOVA, followed by LSD comparison
a = Compared to normal diet protein control, b= Compared to low protein diet control.
p * =<0.01, N S = Not significant.

(ii) Morphological development

(a) Fur onset: The day of appearance of the downing hair did not differ significantly in any of the groups (Table 3).

(b) Pinna detachment: The dietary and Cd exposure schedules had no effect on the day of pinna detachment of the pups (Table 3).

(c) Eye opening: The low protein diet schedule had no significant effect on the day of eye opening but it was significantly delayed in the pups of Cd–exposed, malnourished dams without any significant effect in their protein diet–fed counterparts (Table 3).

(d) Incisor eruption: The dietary and Cd exposure schedules had no significant effect on the day of incisor eruption in the pups (Table 3).

(iii) Surface righting:

No statistically significant effect on the development of surface righting reflex in any of the groups was observed (Table 4).

(iv) Air righting:

The maturation on the air righting reflex was not significantly altered in any of the groups (Table 4).

(v) Visual placing:

A significant delay in the development of the visual placing response was observed only in the pups of the Cd–exposed, malnourished dams (Table 4).

(vi) Cliff aversion:

A significant delay in the maturation of the cliff aversion response was observed in the pups of Cd–exposed dams of both the dietary groups but the effect was more marked in the protein malnourished group (Table 5).

(vii) Swimming behavior:

The maturation of the swimming behavior, as judged by the direction as well as the head angle was significantly retarded in the pups of Cd–exposed dams of both the diet groups but the effect was more marked in the malnourished group especially on the head angle scoring (Table 5).

(viii) Ascending wire mesh:

A significant delay in the development of the criterion response in the ascending wire mesh test was observed in the pups of Cd–exposed malnourished dams only (Table 6).

(xi) Balance beam test:

The development of the beam balancing ability was significantly delayed in the pups of Cd–exposed dams of both the diet groups but the effect was more marked in the protein malnourished group (Table 6).

(x) Day of diet ingestion:

The dietary and Cd–exposure schedules had no significant effect on the day of diet ingestion, (Table 6).

Group	Day of maturation of (reflexes)		
	Surface righting	Visual placing	Air righting
Normal protein diet (control)	6.25 + 0.53	14.43 + 1.29	15.38 + 0.82
Normal protein diet + Cd	6.82 + 0.47 NSa	15.50 + 1.71 NSa	15.67+ 0.94 NSa
Low protein diet (control)	5.64 + 0.26	16.32 + 1.75	15.71 + 1.20
Low protein diet + Cd	6.17 + 0.35NSb	19.93 + 1.13 *b	16.25 + 1.82 NSb

Table 4 Effect of concurrent low protein diet and Cd exposure on certain development indices in F1-pups
Values represent the mean + S.E. of 8–10 pups (litter mate)
Statistical evaluation by one–way ANOVA, followed by LSD comparison
a = Compared to normal protein diet content; b= Compared to low protein control.
p =*<0.05; **< 0.01.
N S = Non significant

Group	Day of maturation of		
	Cliff aversion	Swimming behavior	
		Direction	Head angle
Normal protein diet	8.43 + 0.42	12.72 + 0.91	12.32 + 0.54
Normal protein diet + Cd	9.57 + 0.51 *a	15.37 + 0.42 *a	13.98 + 0.37 *a
Low protein diet	8.32 + 0.35	14.32 + 0.73	13.71 + 0.47
Low protein diet + Cd	11.8 + 0.43 **b	17.52 + 1.07 **b	16.29 + 0.72 *b

Table 5: Effect of concurrent low protein diet and Cd exposure on certain development indices in F1-pups
Values represent the mean + S.E. of 8–10 pups (litter mate)
Statistical evaluation by one–way ANOVA, followed by LSD comparison
a = Compared to normal protein diet content; b= Compared to low protein diet control
p =*<0.05; **< 0.01
N S = Non significant

Day of maturation of		
Wire-mesh ascending	Beam balance	Day of diet ingestion
11.39 + 0.74	16.96 + 0.44	17.56 + 2.25
11.96 + 0.52 NSa	18.82 + 0.23 *a	18.27+ 2.64 NSa
11.89 + 0.45	16.28 + 0.46	18.85 + 2.47
13-07 + 0.62*b	19.93 + 0.38 **b	18.17 + 1.95 NSb

Table 6: Effect of concurrent low protein diet and Cd exposure on certain development indices in F1-pups
Values represent the mean + S.E. of 8–10 pups (litter mate)
Statistical evaluation by one–way ANOVA followed by LSD comparison
a = Compared to normal protein diet content; b= Compared to low protein control
p =*<0.05; **< 0.01

Discussion

In the present study, the low protein diet (8%) caused a significant reduction in the litter size, a delay in the physical developmental landmarks like less body weight and eye opening, and also caused marked delay in the development of sensory–motor reflexes like visual placing, cliff aversion, in the F1 offspring. The viability and lactation indices were not significantly affected.

There is no doubt that protein malnutrition has a very prolonged effect on the behavioral and developmental patterns. Malnutrition imposed during the lactation period on young growing mammals by either food restriction of the administration of a low protein diet significantly delays the development of various psychomotor reflexes [34-36]. In the rat, development indices such as eye and ear opening, grasping reflex, rearing reflex and righting reflex are all significantly delayed. Under nutrition imposed during the gestation period by feeding a very low protein diet (5% casein) has been shown to produce a significant depression in the ontogeny of various psychomotor reflexes in the offspring, in the mice [37] and, in the rat, [34,35,38,39]. The lack of effect of the 8% protein diet employed in the present study, on the viability and lactation indices might be due to the moderate level of protein deficiency induced.

The prenatal exposure to cadmium had no significant effect on the number of pregnancies, litter size and mortality in the rats of either dietary regimen. Also, it had no significant effect on the physical developmental landmarks like fur onset, pinna detachment, and incisor eruption. Such effects on the developmental indices have also been reported with other environmental neurotoxic metals like lead [40],manganese [41] and tin [42]; pesticides like diazenon [9], carbofuran [43], Kepone [11], maneb [44] and industrial solvents like t-butanol [45] and carbon disulphide [46] etc.

In the present study cadmium at la low dose level did not cause any significant effect on diet consumption in either dietary group of Fo–rats during the growing, gestational and lactation periods. Cadmium concentration, as low as 1 ppm in drinking water, has been reported to cause aversiveness in rats [47]. In our current study, the water intake in the cadmium exposed dams was lower than that of the controls but the difference was not statistically significant at any time of exposure. The reason for this anomaly is not clear. The lower body weight, smaller size and the resultant body surface area might be a possible reason.

The cadmium intake in the malnourished animals calculated on body weight basis, did not differ significantly from that of the normal protein diet fed rats which correlates well with the water consumption data.

The growth retarding effect of cadmium is well documented. An

exposure to dose levels, as low as 50 ppm, in drinking water, is known to retard growth in adult rat [48]. In our study, cadmium exposure resulted in significant growth retardation in both the dietary groups of the Fo–generation rats during the growing, gestation and lactation periods. Prenatal exposure to cadmium has been reported to result in decreased birth weight in the offspring [21,49,50]. In our study we found that low protein diet as such and cadmium exposure (in normal protein diet group only) resulted in a significant decrease in the birth weight of the pups. Maternal protein restriction in rats has been stated to retard both placental and fetal growth [51]. It is obvious that protein deficiency causes a decreased birth weight in F1–generation. The mechanism of this developmental toxicity is at present, obscure and needs further investigations.

No significant effect on the viability and lactation indices in the pups of both normal and protein deficient diet fed animals was found. Similar effects have been reported in the Mn treated rats earlier [12]. In the present study we found that the dietary and cadmium exposure schedules has no significantly effect on the number of pregnancies, deliveries or still births. The litter size in the malnourished groups was significantly lower than that of the normal protein diet fed animals but cadmium exposure had no significant effect on the litter size in either dietary group. There have been reports on effect of cadmium toxicity on somatic indices [21]. These authors found significant delay in the development of certain somatic indices like eye opening and air righting reflex in the pups of low protein fed groups. Similar effects of protein malnutrition on the development of somatic indices have been reported earlier in case of other neurotoxic metals like Mn [12] and Pb in normal diet fed rats [26,37]. In the present study, no statistically significant change was observed in fur–onset and pinna detachment in either dietary cadmium exposed group. The low protein diet schedule had no significant effect on the day of eye opening but it was significantly delayed in the pups of cadmium exposed malnourished dams without any significant effect in their protein–diet fed counter parts. The dietary and cadmium exposure schedules had no significant effect on the day of incisor eruption, development of surface and air righting reflexes. A significant delay in the development of the visual placing response was observed only in the pups of the cadmium exposed malnourished dams. Cadmium is reported to effect the development on the cliff aversion response and swimming behavior [21]. We also found a significant delay in the maturation of cliff aversion response in the pups of cadmium exposed dams of both the dietary groups but the effect was more marked in the protein malnourished group. The maturation of the swimming behavior, as judged by the direction as well as the head angle, was significantly retarded in the pups of cadmium exposed dams of both the diet groups but the effect was more marked in the malnourished group especially on the head angle scoring. A significant delay in the development of the criterion response in the ascending wire mesh test was observed in the pups of cadmium exposed malnourished dams only whereas the development of beam balancing ability was significantly delayed in the pups of cadmium exposed dams of both the diet groups but the effect was more marked in the protein malnourished groups. These sensory–motor parameters are indicative of the enhanced toxicity of cadmium on developing neuronal system due to protein malnutrition. The exact mechanism of cadmium induced developmental toxicity still remains a crux and needs to be thoroughly investigated for.

These effects are indicative of cadmium induced interference with the normal development of sensory motor reflexes and motor coordination. Recent work by Webster and Valois [52] has provided a basis for relating behavioral anomalies produced by cadmium treatment to cellular and tissue alterations in the immature brain. However, the deficits in birth weight and growth observed in these cadmium exposed animals should also be taken into consideration since early growth retardation has been shown to result in delayed somatic ontogeny [32,33,53].

Thus, the present study manifests that exposure to even low dose levels of cadmium during the critical periods of development might result in development and behavioral aberrations, and emphasizes the risk of early environmental exposure of man in his early life to this metal. It is also highlighted that these developmental effects are more likely to occur in low protein fed condition than in nutritionally adequate state.

Human being are exposed to an ever increasing concentrations of cadmium via food, water and air, and the exposure of cadmium during the vulnerable developmental and growing stage is likely to induce certain developmental deficits. Changes in the milieu during their early developmental periods play a great role in the evolvement of the full and mature adult behavioral pattern. Often the developmental deficits lead to behavioral aberrations in the adulthood. Our findings of the enhanced vulnerability of the protein malnourished rats assume special significance in view of the prevailing protein deficient conditions in the underprivileged population.

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