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The Effects of Zinc on the Central Dopaminergic System of Rats Prenatally Exposed to Cadmium

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Abstract

On the morning of the first day of pregnancy, Wistar rats were administered a single IP injection of either zinc sulfate (10.0 mg/kg) or saline. For the remainder of pregnancy, half the rats in each group then consumed filtered tap water while the other half consumed filtered tap water with 50 ppm of cadmium ($CdCl_2$). At eight weeks after birth, the behavioral profile of male offspring was assessed in the following way: Apomorphine (non-selective dopamine receptor agonist), (+)-7-hydroxy-2-(di-n-propylamino) tetralin (7-OH-DPAT) (D_3 agonist) and (+/-)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol (SKF 38393) (D_1 agonist) were used to evaluate stereotyped behavior, yawning activity and oral movements – indices for these respective agonists. In addition, two dopamine receptor antagonists, haloperidol (D_2 antagonist) and 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzapine (SCH 23390) (D_1 antagonist) were used to evaluate cataleptogenic activity. Additional behavioral parameters studied were locomotor activity, irritability and reaction to a painful stimulus. Dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 3-methoxytyramine (3-MT) were quantified in the striatum, hippocampus and in the frontal cortex of the brain by means of HPLC/ED technique. In addition, cadmium levels were analyzed in the brain, liver, kidney and bone of newborn rats. Our results indicate that prenatal exposure of pregnant rats to cadmium produced alterations in the reactivity of central dopamine receptors and modulated the level of dopamine and its metabolites in the offsprings' brains. A single injection of zinc, preceding cadmium consumption, attenuated some of the effects of cadmium on the offsprings' dopaminergic system. Zinc also reduced cadmium deposition in the brain, kidney and bone, but enhanced its accumulation in liver. In summary, zinc may exert some neuroprotective effects against cadmium neurotoxicity.

Keywords: zinc, cadmium, 7-OH-DPAT, SKF-38393, apomorphine, haloperidol, SCH-23390, biogenic amines, behavior, rats

Introduction

Cadmium (Cd), a highly neurotoxic agent in animals and humans, is a major contaminant of the environment, due to its high natural abundance and its industrial use. Numerous studies have demonstrated that exposure of mammals, including humans, to inorganic Cd, resulted in a cascade of toxic effects. This is due mainly to binding of the ionic Cd to thiol groups in enzymes, to other proteins, and to nucleic acids in the cell nucleus [1]. Delete-

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rious effects of Cd have been reported in the liver, lungs, kidneys, testes, eyes and intestines of various mammals, and high doses of Cd have been proven to be teratogenic and neurotoxic [2, 3]. Reports on human toxicity are derived mainly from data on inhaled Cd, mostly emanating from industrial fallout, of which Cd is a common pollutant. The developing brain of mammalians is particularly more sensitive to Cd than the adult brain, being affected both morphologically and neurochemically. In adult animals, Cd is deposited in all internal organs, but mainly in the liver, kidney and bone [4].

In previous studies from our laboratory we investigated the ontogenetic effects of Cd (5 and 50 ppm), administered to pregnant rats, alone or in combination with ethanol (10% v/v), for the entire duration of their pregnancies [5]. We demonstrated that female offspring of rats that had been prenatally exposed to Cd, and then acutely injected with ethanol (3.5 g/kg IP), rapidly lost (but only temporarily) their righting reflex as compared to controls not exposed to Cd. In female offspring rats that had been exposed in utero to Cd and ethanol, the concomitantly measured "righting reflex" returned to the control value. No difference from control was found in sleep duration in male rats prenatally exposed to Cd [6]. In another study we observed that exposure of rats to 50 ppm Cd (in drinking water) during pregnancy increased locomotor activity and irritability, but decreased exploratory activity in their male offspring, studied in adulthood [7].

In another study we demonstrated that when pregnant rats consumed 5 or 50 ppm of Cd, the reactivity of central dopamine D_2 receptors in their adult male offspring (as assayed by quinpirole-induced yawning behavior) changed as compared to the control rats [8]. In contrast, prenatal Cd did not modify SKF-38393-induced oral activity, a measure of central D_1 receptor reactivity. Cd affected the production and release of biogenic amines by dopaminergic, noradrenergic and serotoninergic nerves [8-13].

Zinc (Zn) is an essential nutritional and biochemical component of the human body, and its deficiency has severe health consequences. Conversely, excessive exposure to Zn is relatively uncommon, and occurs only under heavy exposure to this metal. Zn does not accumulate in proportion to it consumption, as the body content of Zn is modulated by homeostatic mechanisms that act principally on its absorption and on regulation of its liver levels [14-17].

Zn is easily absorbed from the intestinal tract and is deposited mostly in the liver [15]. More than 200 enzymes from different species, including humans, require zinc for their activity. Among these enzymes are alkaline phosphatase, alcohol dehydrogenase, pancreatic carboxypeptidase, nuclear DNA-dependent RNA polymerase and carbonic anhydrase [6].

In mammals, Zn deficiency during pregnancy can induce teratogenic effects, some behavioral disturbances, and memory deficits in offspring. Zn deficiency in humans causes "Prasad's Syndrome", exemplified by growth retardation and delayed sexual maturation [6, 18]. It has been also suggested that Zn may exert a protective effect against lead and Cd in mammals [6, 19, 20].

In the present study we investigated the effect of a single dose of Zn, administered to pregnant rats who consumed Cd during their entire pregnancy, on the reactivity of their offspring to the central dopaminergic system and receptors to selected agonists and antagonists.

Material and Methods

Pregnant Wistar rats, weighing 200-220 g each, were used for the present study. Rats were housed in a well-ventilated room, at 22±2°C, and were kept under a 12h light: 12h dark cycle. This study was approved and controlled by the local Bioethics Committee for Animals at the Medical University of Silesia. On the morning of the first day of pregnancy, the day vaginal plugs were found, pregnant rats were injected with zinc sulfate ($ZnSO_4 \times 7H_2O$, 10.0 mg/kg IP) in saline (1.0 ml/kg), and were kept one per cage. Rats had free access to pelleted food (Altromin-1324, Lage, Germany) and filtered tap water, which were replaced on the afternoon of this day by water containing 0 (for the control rats) or 50 ppm of cadmium (as $CdCl_2 \times 2H_2O$; POCH Ltd., Gliwice, Poland). The study was comprised of four groups:

(1) saline IP and tap water during pregnancy;
(2) zinc IP and tap water during pregnancy;
(3) saline IP and cadmium during pregnancy; and
(4) zinc IP and cadmium during pregnancy.

Fluid consumption of each pregnant rat was monitored regularly. On the day of parturition, the cadmium-containing water was replaced by tap water, and the number of pups was adjusted (usually reduced) to six per litter, preferably males. Pups were left with their mothers until weaning. On the 21st day after birth all male pups for each of the four groups were pooled, divided 3 per cage and were left untreated until the age of 2 months. At that age the following tests were performed on rat offspring, all between 9:00 AM and 1:00 PM.

Behavioral Study

Spontaneous locomotor activity. Rats were individually placed in transparent glass cages 48x26x36 cm, and were allowed to acclimate for 30 minutes. Then, 1.0 ml/kg saline was injected IP to each rat, and 10 minutes later locomotor activity (time spent walking, sniffing, grooming and rearing) was recorded in seconds, during 10 minutes.

Irritability was evaluated according to Nakamura and Thoenen [21]. The exogenous stimuli were: blowing air on the rat's back, touching its whiskers and its back with a glass rod, and holding the rat by its front paw. Each reaction was evaluated on a 0-3 scale. This test was performed 10 minutes after assessment of locomotor activity.

Exploratory activity. After rats had acclimated to the laboratory environment for 30 minutes, each rat was injected IP with saline, 1.0 ml/kg. Ten minutes later each rat was placed in the center of a wooden platform, 100 cm square, surrounded by a 40-cm fence to prevent escaping. The flat platform had 4 rows of 4 holes each, 7 cm in diameter and 20 cm apart. The number of times (during a three – minute period) that each rat stuck its head beneath the interaural line, into any hole, was counted and recorded [22].

Stereotyped behavior. Rats were individually placed in transparent glass cages 48x26x36 cm, on fresh woodchip bedding, and were allowed to acclimate for 30 minutes. Then, all rats were injected SC with 1.0 mg/kg apomorphine, a non-selective dopamine receptor agonist [23]. Every 15 minutes after the injection, and up to 90 minutes, stereotyped behavior of each rat was measured by the scoring method of Creese and Iversen [24], on a scale of 0-6.

Yawning activity was evaluated by 7-OH-DPAT, according to Kostrzewa and Brus [25]. After one-hour acclimation to the laboratory environment, each rat was injected IP with saline 1.0 ml/kg, and the number of yawns was counted for 60 minutes. Then each rat was injected IP with a low dose (0.032 mg/kg) of 7-OH-DPAT (a selective D_3 receptor agonist) [26], and the number of yawns was counted for an additional 60 minutes. The same male rats were challenged on subsequent days with escalating doses of 7-OH-DPAT (0.065, 0.130 and 0.260 mg/kg), one dose per day, and were observed as above.

Oral movements (vacuous chewing) were evoked by SKF-38393, a selective central D_1 agonist [27-29]. After acclimating to the lab environment, rats were injected with SKF-38393 in escalating daily doses of 0; 0.1; 0.3 or 1.0 mg/kg IP.

Cataleptogenic activity was evaluated as described by Kostrzewa and Kastin [30], using 0.5 mg/kg IP of haloperidol, a selective central D_2 antagonist [31] and 0.5 mg/kg IP SCH-23390, a selective central D_1 receptor antagonist [32], or saline. Each rat in its turn was placed on a 25x50 cm wire mesh screen, forming 1x1 cm squares, and was inclined by 60° to the horizontal plane. The time (in seconds) taking each rat to move any paw along at least one screen division within 60 second was recorded. Measurements were performed 5 times: at 15, 30, 45, 60 and 90 minutes, and results of each observation were summarized.

The reaction to a painful stimulus was performed using a hot plate technique. Each rat was placed on a 28x28 cm copper plate, maintained at 55°C and enclosed within plexiglas walls. The time interval between the moment when a rat had all four paws on the plate, and when it started to shake or lick one of its paws, was recorded in seconds. Each recording started 10 minutes after IP saline administration, and was repeated 3 times, with 10 minutes intervals. Results are expressed as the mean of the three measurements [33].

Locomotor coordination. After 30 minutes of acclimation to the laboratory condition, rats were injected IP with saline (1.0 ml/kg). Ten minutes later each rat was placed on a wooden bar 3 cm in diameter. The bar rotated longitudinally five times per minute, and the length of time (in seconds) each rat managed to stay on the rotating bar was recorded. A rat that stayed on the bar for 300 seconds was taken off. This test was carried out on each rat twice, at 30 minute intervals, and the mean time was calculated for each rat.

Biochemical Estimations

Biogenic amines assay. Two-month old male offspring from all four study groups were sacrificed by decapitation, and the brains were immediately excised and placed on ice. The striatum, hippocampus and frontal cortex were separated, placed on dry ice, weighed and stored at -70°C, pending assay. Dopamine (DA), 3,4-dihydroxy--phenylacetic acid (DOPAC), homovanillic acid (HVA) and 3-methoxytyramine (3-MT) were assayed by an HPLC/ED technique [34].

Cd assay. Newborn rats from each of the four groups were sacrificed, and their brains, livers, kidneys, and mandible bones were removed and cleansed of blood. About 100 mg of each tissue (accurately weighed) was dissolved in 1.0 ml of ultra-pure nitric acid, and the Cd content was assayed using an SP-2900 Pye Unicam AA (Cambridge, UK) atomic absorption spectrometer, and handled according to the Company instructions [35].

Each group for the behavioral study consisted of 9 rats, and each group for biochemical analysis consisted of 4-5 rats (tissues).

Statistical Analyses

Data from each behavioral or biochemical study were analyzed by two-way ANOVA and post-ANOVA tests of Neuman-Kuels. Differences in p values of <0.05 were considered significant.

Results

Daily water consumption. Rat groups 3 and 4, which consumed Cd-containing water, drank significantly less water than groups 1 and 2, which drank tap water (Table 1).

Irritability. Rat groups #2 and #3, deriving from dams that consumed Cd or were injected with Zn had irritability values greater than controls (Table 1). The Cd group injected with Zn was not different from control.

Reaction to pain stimulus. Time to react to a pain stimulus (hot-plate test) was longest in the control group. Rat group 4 (Zn plus Cd) had a significantly shorter reactivity period as compared to control group #1 (saline and tap water) ($p<0.05$) (Table 1).

Spontaneous locomotor activity was higher in rats prenatally pretreated with Cd or Zn as compared to the

Table 1. Daily fluid consumption by pregnant rats, irritability scores and reaction to pain stimulus in rats prenatally exposed to cadmium and zinc (x ± SEM; n = 9).

Group number	Treatment	Fluid consumption ml/100 g BW/day	Irritability (score, 0-3 scale)	Pain stimulus (in seconds)
		Pregnant rats	Adult offspring	
1	Saline IP + Tap water	13.8 ± 0.8	2.1 ± 0.6	13.2 ± 1.1
2	Zinc IP + Tap water	14.1 ± 1.0	2.9 ± 0.3	12.3 ± 0.7
3	Saline IP + Cadmium 50 ppm	10.2 ± 0.6*	2.8 ± 0.2	11.8 ± 0.4
4	Zinc IP + Cadmium 50 ppm	11.1 ± 0.4*	1.9 ± 0.5^{+}	9.1 ± 0.6*

Explanation: * $p<0.05$ as compared to group 1 and 2; $^{+}$ $p<0.05$ as compared to group 3.

Table 2. Locomotor activity, exploratory activity, and coordination ability in rats prenatally exposed to cadmium and zinc (x ± SEM; n = 9).

Group number	Treatment	Locomotor activity (seconds)	Exploratory activity (number of dippings)	Coordination ability (seconds)
1	Saline IP + Tap water	262.1 ± 58.2	2.7 ± 0.6	88.6 ± 35.2
2	Zinc IP + Tap water	385.7 ± 57.0	2.9 ± 0.4	42.3 ± 6.2
3	Saline IP + Cadmium 50 ppm	423.9 ± 33.5*	2.8 ± 0.7	34.3 ± 6.8*
4	Zinc IP + Cadmium 50 ppm	274.4 ± 50.1^{+}	2.3 ± 0.5	54.2 ± 7.1

Explanation: * $p<0.05$ as compared to group 1; $^{+}$ $p<0.05$ as compared to group 3.

Table 3. Catalepsy, evaluated by SCH 29390 and haloperidol injection in rats prenatally exposed to cadmium and zinc (x ± SEM; n = 9).

Group number	Treatment	SCH 29390 0.5 mg/kg (seconds)	Haloperidol 0.5 mg/kg (seconds)
1	Saline IP + Tap water	2.7 ± 0.6	35.4 ± 3.9
2	Zinc IP + Tap water	2.9 ± 0.4	69.2 ± 10.5
3	Saline IP + Cadmium 50 ppm	164.6 ± 23.4*	91.6 ± 11.5*
4	Zinc IP + Cadmium 50 ppm	92.5 ± 25.9^{+}	58.0 ± 9.8

Explanation: * $p<0.05$ as compared to group 1; $^{+}$ $p<0.05$ as compared to group 3.

control (423.9 ± 33.5 and 385.7 ± 57.0 vs 262.1 ± 58.2 respectively). In the Cd group pretreated with Zn, locomotor activity was no different from control (Table 2).

Exploratory activity, expressed in numbers of dipping during 3 minutes of observation, was similar in all four examined groups (Table 2).

Locomotor coordination, expressed in seconds, was shortest in the Cd group pretreated with Zn (Table 2).

Cataleptogenic activity, induced by SCH 23390, was higher in rats exposed to Cd parentally or to Zn (alone) prenatally (Table 3). In rats derived from dams that consumed Cd and also injected with Zn, catalepsy values were no different from control (Table 3).

Haloperidol induced the longest catalepsy time in those rats prenatally exposured to Cd, as compared to the control group (Table 3). In the two other examined groups (Zn, and Cd plus Zn) catalepsy time was shorter as compared to the group exposed to Cd only; but, greater than control.

Yawning activity. The average number of yawns after saline injection in all examined groups ranged, on average, from 2.0 and 4.8; and steadily increased after 7-OH-DPAT, up to a dose of 0.130 – 0.260 mg/kg. The greatest increase was observed in the control group (saline and tap water), and the lowest yawning number was observed in rats exposed to Zn alone (Fig. 1). Numbers of yawns after 7-OH-DPAT (0.130 mg/kg) in the Cd group and in the Zn plus Cd groups was in between the values in control rats and Zn (alone) groups of rats (Fig. 1).

Oral movements. There was a gradual increase in the

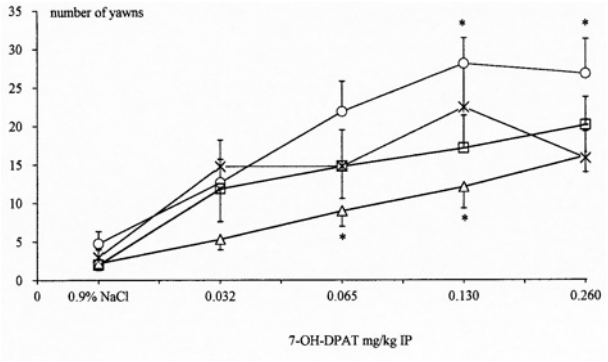

Fig. 1. Yawning behavior after 7-OH-DPAT injections in rats prenatally exposed to cadmium and zinc (x/SEM; n = 9).
Explanation: 1. – *- Control; 2. – Δ – Zinc 10.0 mg/kg IP; 3. – ○ – Cadmium 50 ppm; 4. – □ – Zinc 10.0 mg/kg IP + Cadmium 50 ppm. *p<0.05 1/3; + p<0.05 2/3; ○ p<0.05 1/2; □ p<0.05 3/4

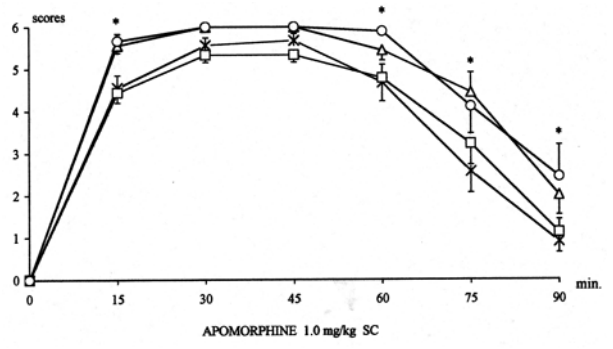

Fig. 2. Stereotyped behavior after apomorphine (1.0 mg/kg SC) injection in rats prenatally exposed to cadmium and zinc (x ± SEM; n = 9)
Explanation as in Fig. 1.

number of oral movements in all four groups tested after SKF 38393 challenges, without statistical differences between groups (results not presented).

Stereotyped behavior. Scores for stereotyped behavior peaked in all four groups at 30 to 60 minutes after apomorphine administration, then gradually declined. Differences between the scores of the four groups were minimal (Fig. 2). Only at 15, 60 and 90 seconds of observation was the intensity of stereotyped behavior significantly lower in groups exposed to Zn plus Cd as compared to Cd alone (Fig. 2).

Catecholamine assay. DA levels increased significantly by about 30% in the striatum of rats prenatally exposed to Cd, vs. control (Fig. 3). In the groups exposed to Zn (with or without Cd exposure) striatal DA content was less than that of the Cd (alone) group but higher than control. No differences in striatal levels of DOPAC, HVA, or 3-MT were observed between the four groups (Fig. 3).

In the frontal cortex DA level was highest in the group of rats prenatally injected with Zn (alone). In the Cd group exposed to Zn pretreatment the DA level in cortex was no different from control (results not presented). There was no difference among the four groups in DA, DOPAC, HVA and 3-MT level in the hippocampus.

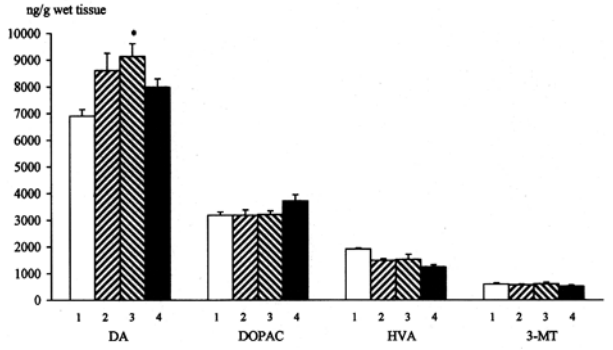

Fig. 3. Biogenic amine levels in the striatum of rats prenatally exposed to cadmium and zinc (x ± SEM; n = 6)
1. – Control; 2. – Zinc 10.0 mg/kg IP; 3. – Cadmium 50 ppm; 4. – Zinc 10.0 mg/kg IP + Cadmium 50 ppm.

Cadmium assay. In all four examined groups the highest accumulation of Cd in the brain, liver, kidney and bone was observed in rats prenatally exposed to Cd (Table 4). Zn injected to the dams immediately before pregnancy prevented the accumulation of Cd in brain, kidney and bone, but increased Cd level in the liver.

Table 4. The level of cadmium (μg/g) in the brain, liver, kidney and bone of newborn rats prenatally exposed to cadmium and zinc (x ± SEM; n = 4-5).

Group number	Treatment	Brain	Liver	Kidney	Bone
1	Saline IP + Tap water	5.9 ± 1.1	19.9 ± 6.0	15.7 ± 1.2	11.3 ± 6.1
2	Zinc IP + Tap water	11.4 ± 8.5	21.8 ± 9.5	21.8 ± 12.6	19.1 ± 3.0
3	Saline IP + Cadmium 50 ppm	10.3 ± 1.3	25.7 ± 4.7	31.9 ± 18.4	35.4 ± 27.4
4	Zinc IP + Cadmium 50 ppm	2.7 ± 0.3*	38.6 ± 22.3	10.5 ± 1.8*	4.5 ± 0.3*

Explanation: * p <0.05 as compared to group 3.

Discussion

Cd salts in the diet and in the environment are well absorbed from the mammalian intestinal tract. Between 4% and 25% of the intake of Cd is absorbed, depending on concentration, exposure time, and animal species [36]. Barriers for Cd transport, such as the placenta, are composed of layers of trophoblastic cells, where metalothioneine is synthesized. Metalothioneine is also synthesized by the fetal liver, this being the major reason for accumulation of Cd by fetal liver [37]. Absorption of Cd is much more profound in the younger pups than in the older rats, emphasizing the significant transfer of this pollutant metal via the milk of the nursing mothers [38]. In the present study the transfer of Cd into the pups was only during pregnancy, and possible variations in tissue levels of Cd are attributed to the age of the offspring [4].

The developing brain is affected by Cd, and numerous morphological, biochemical and behavioral changes have been reported in mammalian fetuses and pups after Cd consumption by their pregnant mothers [39, 40].

There is only sporadic data concerning the effect of Cd on the central neurotansmitter systems in mammals. Hrdina et al. [41] demonstrated that Cd increased DA concentration in the striatum of rats, but that 5-HT content was decreased in the brain stem. Others also demonstrated that Cd generally increased DA, and decreased 5-HT metabolism in different parts of mammalian brain [10, 42-44]. Rastogi et al. [12] found that daily exposure of rats to Cd (1.0 mg/kg for 30 days) enhanced the level of DA in the hypothalamus. Antonio et al. [45, 46] reported that gestational administration of Cd produced a significant DA increase in mesencephalon. Others have observed that Cd injection ($CdCl_2$, 1.0 mg/kg) for 5 days to nursing rats increased DA release by about 180% in 13-day-old animals [47]. In our other study [48] we found that prenatal Cd (50 ppm) exposure increased DA level in the striatum as compared to the control (9.647 and 8.194 ng/g of wet tissue respectively) without changes in the DOPAC level. In the present study we confirmed previous results.

The central nervous system has been demonstrated to have a variety of receptor subtypes of D_1 and D_2. As both types of dopamine receptors are involved in behavioral, neurobiological and psychotic disorders, many of their agonists and antagonists have been used for treating mental disturbances. In addition, selective agonists such as SKF 38393 and 7-OH-DPAT, and antagonists such as haloperidol and SCH 23390, have been widely used as pharmacological tools.

SKF-38393 is an agonist at the D1 receptor complex, which includes D_1 and D_5 (D_1-like) receptor subtypes. The D_1 subtype is associated with SKF 38393-induced oral activity in rats, and this has been demonstrated to be a sensitive method for evaluating its binding [28, 49]. 7-OH-DPAT has been shown to be an agonist of the D_3 and dopamine D_2 receptor subtypes of the D2 receptor complex. The D_3 receptor subtype has also been implicated in 7-OH-DPAT-induced yawning behavior. It has therefore been suggested that D_3 receptor subtype may be the most important of the D_2 receptor isoforms, which is involved in their activities [26, 50]. For this reason we have used oral movement and yawning activity (induced by dopamine agonists), to assess the reactivity of dopamine receptors following prenatal exposure to Cd.

The present study indicates that reactivity of D_3 (D_2-like) receptors in the offspring of mothers that consumed 50 ppm Cd in their drinking water during pregnancy, was reduced vs. control. Conversely, Cd did not alter reactivity to SKF 38393, the D_1-selective agonist. This is in agreement with our previous finding [8]. However, the mechanism by which Cd alters dopamine receptor sensitivity, especially facilitating haloperidol and SCH 23390 catalepsy, is still unclear. It has been suggested that there were changes in the density and affinity of these receptors, and that Cd alters DA synthesis and other neurotransmitter systems in the brain of mammals.

Zn is an essential nutritional element, involved in the activity of many enzymes and in a variety of biochemical processes. Zn deficiency in humans was first characterized by Prasad et al. [51] in adolescent Egyptian boys with retardation of growth and with delayed sexual maturation. This deficiency may be accompanied by protein-caloric malnutrition, pellagra, and deficiency of iron. Dietary inadequacies of Zn, coupled with liver disease, such as from chronic alcoholism, may be associated with dermatitis, night blindness, testicular atrophy, impotence and poor wound healing. Other chronic clinical disorders attributable to Zn deficiency are ulcerative colitis, malabsorption syndrome, chronic renal disease and hemolytic anemia. Zn deficiency in the newborn may be manifested by dermatitis, loss of hair, impaired healing, susceptibility to infection, and some neuropsychologic abnormalities [15, 16, 18].

Zn overdose from excessive ingestion is uncommon, and results mostly from inhalation of zinc fumes during industrial processes. It may cause respiratory problems, fever, weakness, nausea and vomiting [6, 15].

Zn can interact with other metals such as copper, iron, manganese, Cd and lead [52]. Administration of Zn together with lead decreases the hepatic and renal uptake of lead, and reduces the lead-induced inhibition of delta-aminolevulonic and dehydratase activity in serum [6]. Increased dietary Zn reduced the levels of lead and other metals in blood and tissues, and its toxicity in mammals [19, 20]. Conversely, we found that Zn injection also induces some changes in the central dopaminergic system of adult rats.

Previously we demonstrated that a single injection of Zn, administered prior to intrauterine intoxication with lead, interacted with the effects of lead on central neurotransmitter receptors. We demonstrated that Zn prevented some changes in the reactivity of central dopaminergic D_2 receptors in the brain in those animals. In addition, Zn prevented some lead-induced changes at the DA level

in the striatum of rat offspring. Zn also prevented the deposit of lead in the liver of rat offspring, prenatally exposed to lead [53].

In the present study we stated that a single injection of Zn prior to intrauterine intoxication with Cd, attenuated some effects of Cd on the central dopaminergic system. However, effects are not dramatic, as is the effect of Zn on lead neurotoxicity and its deposit in the rat body [53].

In summary, Zn administration prior to Cd intoxication produced altered dopamine D_2 receptor reactivity, spontaneous locomotor activity, SCH-23390-induced catalepsy, and DA content of striatum. Zn administration in pregnancy, prior to prolonged Cd administration, reduced Cd deposition in the brain.

To the best of our knowledge, no data have yet been published concerning Zn and Cd interaction in the central dopaminergic system of mammals. Zn may have exerted a protective role on the central dopaminergic system of rats exposed to Cd during intrauteral development. It is likely that brain metallothionein, (mainly MT III) plays an important role in this mechanism [54].

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