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Short Communication

Effect of Zinc on [^{3}H]Thymidine, [^{3}H]Uridine and [^{3}H]Glicine Incorporation in the Tissues of Rats Prenatally Exposured to Cadmium

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Abstract

On the 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 (Cd (CH_3COO_2). At eight weeks after birth both groups were injected with [^{3}H]thymidine (incorporated to DNA) or [^{3}H]uridine (incorporated to RNA) or [^{3}H]glicine (incorporated to protein) 1 μCi/kg IP. Four hours later rats were sacrificed by decapitation and parts of the brain and peripheral tissues were excised and examined for radioactivity in a liquid scintillation counter. Results were presented as a desintegration per minute – DPM/100 mg wet tissue weight, which expressed labeled substances incorporation. Prenatal cadmium exposure decreased incorporation of thymidine, uridine, and glicine in all examined tissues and organs. A single injection of zinc, preceding cadmium consumption, attenuated the effects of cadmium on incorporation of examined substances in peripheral organs, mostly liver, kidney, and pancreas. We concluded and confirmed our previous founding that a single zinc inection prior to cadmium exposure prevents some of its toxic effects on DNA, RNA, and protein synthesis in peripheral tissues of mammals.

Keywords: cadmium, zinc, [^{3}H]thymidine, [^{3}H]uridine, [^{3}H]glicine, 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 cadmium, result in a cascade of toxic effects. This is due mainly to binding of the ionic cadmium to thiol groups in enzymes, to other proteins, and to nucleic acids in the cell nucleus [1]. Reports on human toxicity are derived mainly from data on inhaled cadmium, mostly emanating from industrial fallout, of

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which cadmium is a common pollutant. The developing mammalian brain is particularly more sensitive to cadmium than the adult brain, being affected both morphologically and neurochemically. In adult animals, cadmium is deposited in all internal organs, but mainly in the liver, kidney, and bone [2].

In previous studies we demonstrated that when pregnant rats consumed 5 or 50 ppm of cadmium, the reactivity of central dopamine D_2 receptors in their male offspring (as assayed by quinpirole-induced yawning behavior) changed as compared to the control rats. In contrast, prenatal cadmium did not modify SKF-38393-induced oral activity, a measure of central dopamine D_1 receptor reactivity [3]. Cadmium affected production and release of biogenic amines by dopaminergic, noradrenergic, and serotoninergic nerves [1].

Zinc (Zn) is an essential nutritional and biochemical component of the human body, and its deficiency has severe health consequences. Conversely, excessive exposure to zinc is relatively uncommon, and occurs only under heavy exposure to this metal. Zinc is easily absorbed from the intestinal tract and is deposited mostly in the liver. Zinc does not accumulate in proportion to its consumption, as the body content of zinc is modulated by hoemostatic mechanisms that act principally on its absorption and on regulation of its liver levels [4].

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 [4, 5]. Zinc deficiency in humans causes "Prasad Syndrome," exemplified by growth retordation and delayed sexual maturation [6].

Zinc exerts a protective effect against lead and cadmium in mammals, and we have confirmed above data [7, 8]. A single injection of zinc, preceding cadmium exposure during pregnancy (Cd 50 ppm in drinking water), attenuated some of the discriminative effects of cadmium on the offsprings' central dopaminergic system. Zinc also reduced cadmium deposition in the brain, kidney, and bone, but enhanced its accumulation in liver [7]. Additional data presented that zinc supplementation ameliorated induction by low-frequency electromagnetic field increased lipid peroxidation in the brain of rats [9].

In the present study we investigated the effect of a single dose of zinc, administered to pregnant rats consuming cadmium during their entire pregnancy on the [^{3}H]thymidine (incorporated to DNA), [^{3}H]uridine (incorporated to RNA) and [^{3}H]glicine (incorporated to protein) incorporation in the different tissues and organs of adult rats.

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±2ºC, and were kept under a 12 h light: 12 h dark cycle. This study was approved and controlled by the local Bioethics Committee for Animals of the Medical University of Silesia (decision No. 24/02 issued on 12.09.2002). On the morning of the first day of pregnancy, the day vaginal plugs were found, pregnant rats were injected with zinc sulfate ($ZnSO_4 \cdot 7H_2O$; 10.0 mg/kg IP) in saline (1.0 ml/kg), and were kept one per cage. Rats had free access to pelleted food and tap water that was replaced on the afternoon of this day by water containing 0 (for the control rats) or 50 ppm of cadmium (Cd $(CH_3COO)_2$; POCH Ltd., Gliwice, Poland). The study was comprised of four groups:

(1) saline IP and tap water during pregnancy (no cadmium in the drinking water);
(2) saline IP and cadmium during pregnancy (50 ppm in the drinking water);
(3) zinc IP and tap water during pregnancy (no cadmium in the drinking water);
(4) zinc IP and cadmium during pregnancy (50 ppm in the drinking water).

On the day of parturition, the cadmium-containing water was replaced by tap water. 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 biochemical assays were performed.

Biochemical Estimations

At two months male rats from each group were placed in individual cages for one hour for adaptation to the new environment. Then animals from each group were injected intraperitoneally (IP) with 6-^{3}H-thymidine or 6-^{3}H-uridine or 6-^{3}H-glicine at doses of 1 μCi/kg BW, applied in 0.2 ml volume of manufactured aquaeous solution. The substances were purchased from Amersham Radiochemicals, Pittsburg, PA, USA. Four hours later animals were sacrificed by decapitation. The brain was immediately excised and placed on ice. Then following parts were separated (50-100 mg): frontal cortex, striatum, thalamus with hypothalamus, hippocampus, pons, and cerebellum. Additional following samples of peripheral tissues or organs were separated: heart, skeletal and tongue muscles, pancreas, liver, kidney, and skin. Fragments of the tissues were weighed and placed in 20-ml scintillation vials. One ml of Soluene-350 (Packard Inc., Downers Growe, IL, USA) was added to each vial. Then the tightly-closed vials were incubated at 37ºC for 48 h, until the tissues were completely solved. After that, 10 ml of scintillation cocktail Dimilume-30 (Packard Inc., Downers Growe, IL, USA) was added and the vials were briefly vortexed and placed in a scintillation counter (Liquid Scintillation Counter, DSA 14091, Wallac, Finland). Radioactivity was assessed twice for 2 minutes each time and the final results after removing the background and efficiency of the counter were presented as DPM (disintegration per minute) per 100 mg of wet tissue. The results from each group (6 rats – tissues) were presented as a mean and standard deviation (x±SD). For details see Konecki et al. [10].

Table 1. Effect of zinc and cadmium neonatal exposure on radioactivity after [³H]thymidine 1 μCi/kg IP injection in the peripheral tissues of rats expressed as a DPM/100 mg of wet tissue (x±SD; n=6).

No.	Tissue	Control	Cadmium	% of control	Zinc + Cadmium	% of control	Zinc	% of control
7	Heart muscle	894±63	619±96*	69.2	755±102	84.5	783±58	87.5
8	Sceletal muscle	1,116±84	771±59*	69.1	827±77*	74.1	892±41*	79.9
9	Tongue muscle	1,710±266	1286±76*	75.2	1,180±115	69.0	1,611±53	94.2
10	Pancreas	2,742±322	1,114±134*	40.6	1,696±74^{+}	61.9	1,746±403*$^{+}$	63.7
11	Liver	1,096±83	627±70*	57.2	802±59^{+}	73.2	941±87^{+}	85.9
12	Kidney	2,273±91	1,879±75*	82.7	2,706±548*$^{+}$	119.0	2,195±120^{+}	96.6
13	Skin	1,003±240	874±65*	87.1	798±75*	79.6	1,017±98^{+}	101.4

*p<0.05 versus Control
$^{+}$p<0.05 versus Cadmium
$^{\#}$p<0.05 versus Zinc + Cadmium
DPM – Desintegrations Per Minute

Statistical analysis was performed using Kruskal-Wallis and Behrenso-Fischer tests. For this reason the PS IBM Computer was used. The value of p<0.05 was considered to be significant.

Results

Radioactivity in the brain after [³H]thymidine apply was not estimated in this experiment because of its incorporation to nucleonic during phase S of the mitosis, which does not occur in the brain. Neonatal exposure of rats with cadmium significantly decreased incorporation of [³H]thymidine in all examined peripheral tissues and organs as compared to the respective control (Table 1). Injection of zinc before cadmium intoxication prevented the above effect in the pancreas, liver, and kidney of adult rats.

Zinc alone generally does not modify [³H]thymidine incorporation into examined tissues versus control, except skeletal muscle and pancreas, where it was decreased (Table 1).

Prenatal exposure with cadmium significantly decreased [³H]uridine incorporation in all examined parts of the brain and peripheral tissues as compared to respective controls (Table 2). Injection of zinc prior to cadmium expo-

Table 2. Effect of zinc and cadmium neonatal exposure on radioactivity after [³H]uridine 1 μCi/kg IP injection in the brain and peripheral tissues of rats expressed as a DPM/100 mg of wet tissue (x±SD; n=6).

No.	Tissue	Control	Cadmium	% of control	Zinc + Cadmium	% of control	Zinc	% of control
1	Frontal cortex	1,470±43	1,325±48*	90.1	1,273±57*	86.6	1,418±88	96.5
2	Striatum	1,659±62	1,414±50*	85.2	1,434±54*	86.4	1,554±52	87.6
3	Thalamus with hypothalamus	1,577±147	1,338±88*	84.8	1,409±67	89.3	1,538±73	97.5
4	Pons	1,356±65	1,197±55*	88.3	1,096±90*	80.8	1,420±67$^{+\#}$	104.7
5	Hippocampus	1,560±43	1,348±57*	86.4	1,488±168	95.4	1,437±70	92.1
6	Cerebellum	1,392±59	1,203±64*	86.4	1,263±62*	90.7	1401±52$^{+\#}$	100.6
7	Heart muscle	1,037±47	863±106*	83.2	1,044±73^{+}	100.7	854±62* $^{\#}$	82.4
8	Skeletal muscle	1,556±58	1,099±42*	70.6	1,433±91^{+}	92.8	1,488±31^{+}	95.6
9	Tongue muscle	2,113±54	1,501±90*	71.0	1,481±61*	70.1	1,726±62* $^{\#}$	81.7
10	Pancreas	2,022±158	1,604±180*	79.3	1,564±350	77.3	1,941±658	96.0
11	Liver	1,292±91	968±59*	74.9	1,200±60^{+}	92.9	1,150±435	89.0
12	Kidney	2,537±53	2,056±52*	81.0	2,380±93^{+}	93.8	1,920±435	75.7
13	Skin	1,593±46	1,431±83*	89.8	1,515±118	95.1	1,545±87	97.0

Explanations as in Table 1.

Table 3. Effect of zinc and cadmium neonatal exposure on radioactivity after [^{3}H]glicine 1 μCi/kg IP injection in the brain and peripheral tissues of rats expressed as a DPM/100 mg of wet tissue (x±SD; n=6).

No.	Tissue	Control	Cadmium	% of control	Zinc + Cadmium	% of control	Zinc	% of control
1	Frontal cortex	1,119±80	807±76*	72.1	787±82*	70.3	908±48*	81.1
2	Striatum	1,017±126	833±107	81.9	827±57*	81.3	1,082±68$^{+\#}$	106.3
3	Thalamus with hypothalamus	1,180±97	963±105*	81.6	952±78*	80.7	1,129±66$^{+\#}$	95.7
4	Pons	1,011±77	771±86*	76.3	781±82*	77.3	913±79	90.3
5	Hippocampus	1,023±84	921±90	90.0	872±84	85.2	1,037±43$^{\#}$	101.4
6	Cerebellum	1,005±77	859±68*	85.5	712±57*	70.8	857±73	85.3
7	Heart muscle	894±63	619±96*	69.2	755±102	84.5	783±58	87.5
8	Skeletal muscle	1,116±84	771±59*	69.1	827±77*	74.1	892±41*	79.9
9	Tongue muscle	1,710±266	1,286±76*	75.2	1,180±115*	69.0	1,611±53 $^{+\#}$	94.2
10	Pancreas	2,742±322	1,114±134*	40.6	1,696±74*$^{+}$	61.9	1,746±403*$^{+}$	63.7
11	Liver	1,096±83	627±70*	57.2	802±59*$^{+}$	73.2	941±87^{+}	85.9
12	Kidney	2,273±91	1,879±75*	82.7	2,706±548^{+}	119.0	2,195±120$^{+\#}$	96.6
13	Skin	1,142±89	982±87*	86.0	1,191±86^{+}	104.3	1,220±44^{+}	103.8

Explanations as in Table 1.

sure prevented a decrease of [^{3}H]uridine incorporation in heart and skeletal muscles, and in the liver and kidney as compared to respective controls (cadmium) (Table 2). Zinc in the single injection modified incorporation of [^{3}H]uridine in a different way in heart and tongue muscles of adult rats as compared to respective controls (Table 2).

Neonatal exposure of rats to cadmium decreased incorporation of the [^{3}H]glicine to all examined tissues (except striatum and hippocampus) in adult animals as compared to the respective controls (Table 3). A single injection of zinc to female rats before cadmium exposure prevent its diminished effect on incorporation of [^{3}H]glicine in the pancreas, liver, kidney, and skin only as compared to respective controls (cadmium) (Table 3). A single injection of zinc modified incorporation of [^{3}H]glicine in the frontal cortex, skeletal muscle, and pancreas (Table 3).

Discussion

The influence of cadmium exposure on DNA, RNA, and protein synthesis have been studied since the 1970s. However, usually individual organs were examined, mostly liver, kidney, or lung. Furthermore, experimental animals usually were subjected directly to cadmium exposure, so the issue of transplacental action of metal was not addressed. Cadmium is absorbed from the mammalian intestinal tract in the range between 4% to 25% of the intake metal, depending on its concentration in food, exposure time, and animal species. Cadmium enters fetal circulation through the placenta. Due to metalothioneine produced by trophoblasts in the placenta, accumulation of metal by that organ occurred and concentration of cadmium in human umbilical cord blood vessels is reduced by up to 40-70% of values of maternal blood [11].

Absorption of cadmium 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 [12]. In the present study the transfer of cadmium into the pups was only during pregnancy, and possible variations in tissue levels of cadmium are attributed to the age of the offspring [2].

In our previous experiment we found that prenatal exposure to cadmium increased the content of examined metal in the brain, liver, kidney, and bone of newborn rats versus control and zinc injected prior to cadmium exposition decreased cadmium deposition in the brain, kidney, and bone, but enhanced in the liver [7]. Because of the above data, in the present experiment the cadmium level in the organs of newborn rats was not estimated. Similar results were obtained with zinc and lead. A single injection of zinc administered prior to intrauterine intoxication with lead prevented the deposit of lead in the liver of rat offspring, prenatally exposed to metal and interacted with the effects of metal on the central dopaminergic system [8].

An important tissues protein with high affinity for cadmium is metallothionein which forms chelates with metal. This binding is considered to represent an important means for detoxication or transport of cadmium. This protein is present in rat placenta and fetuses. Moreover, cadmium is an effective inducer of metallothionein. Zinc also induces metallothionein production in a dose-dependent manner mostly in the liver and placenta and protecs against cadmium toxicity [13-17].

Thymidine is a precursor of DNA and incorporated only into cells that are in phase S of the cycle. The intensity of thymidine incorporation into the tissues represents their mitotic activity [17]. In this experiment we presented that cadmium exposure during prenatal development attenuated DNA synthesis in many tissues and peripheral organs of adult rats. Zinc injected in a single dose prior to cadmium exposure prevents toxic effects of cadmium on DNA synthesis in pancreas, liver, and kidney.

Uridine is a precursor of RNA, and the intensity of its incorporation in tissues represents the rate of RNAs and proteins synthesis. It must be added that many forms of RNA exist in mammalians organisms. The mRNA represents 0.5-1.0% of total RNA, being very active biologically. Fraction tRNA represents about 15% of the total RNA, and iRNA about 80% of the cells' RNA [18]. This measurement of uridine incorporation represents general effects only, without the possibility to interpret which form of RNA is mostly affected. Anyway, in the present experiment we found that cadmium prenatal exposure decreased [^{3}H]uridine incorporation in all examined tissues of adult rats. Injection of zinc before cadmium exposure prevents the effects of cadmium in the heart and skeletal muscle, and in liver and kidney.

Glicine is an important aminoacid, an element of many proteins and enzymes in mammalian organisms [18]. Intensity of incorporation of this aminoacid represents protein synthesis and metabolism rate in the tissues. In the present experiment prenatal exposure to cadmium decreased incorporation of [^{3}H]glicine in all examined tissues and organs of adult rats. Zinc in a single dose prevented this effect in the pancreas, liver, kidney, and skin. Zinc does not prevent cadmium's effect on incorporation of labeled uridine and glicine in examined parts of the brain of adult rats.

There are scarce data concerning the effects of cadmium on incorporation of above-examined substances into mammalian tissues and organs. Holt and Webb presented that cadmium injected into pregnant rats inhibited protein synthesis and [^{14}C]thymidyne incorporation into fetal DNA [19]. Similar effects of cadmium on [^{3}H]thymidine incorporation was observed in several organs of adult mouse by others [20]. There are also opposite data. Cadmium increased DNA synthesis by increasing [^{3}H]thymidine uptake into isolate murine macrophages [21].

Cadmium decreased cellular uptake of uridine and its incorporation to RNA in murine lymphocytes [21]. Also, in our previous studies we presented that cadmium diminished the synthesis of RNA much more prominently than protein in offspring rats when it was applied during pregnancy. Labeled with tritium uridine and alanine, incorporation into the mouse heart muscle was decreased by cadmium as compared to the control [10].

It must be added that a single injection of zinc before pregnancy also induced some changes in incorporation of labeled substances in a few examined tissues and organs of adult offspring rats, but that phenomenon was not commented on in the present project. Some data concerning prenatal exposure of rats with zinc on biochemical and behavioral changes in adult animals were presented previously [7, 8].

From this experiment we concluded and confirmed that single injections of zinc preceding cadmium consumption by pregnant rats attenuated the effects of cadmium on the offsprings' DNA, RNA, and protein synthesis. The above effect was exerted in peripheral organs, mostly such as liver and kidney, where the rate of synthesis of nucleotides and proteins is intensive.

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