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Review

CADMIUM TOXICITY REVISITED: FOCUS ON OXIDATIVE STRESS INDUCTION AND INTERACTIONS WITH ZINC AND MAGNESIUM

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Discovered in late 1817, cadmium is currently one of the most important occupational and environmental pollutants. It is associated with renal, neurological, skeletal and other toxic effects, including reproductive toxicity, genotoxicity, and carcinogenicity. There is still much to find out about its mechanisms of action, biomarkers of critical effects, and ways to reduce health risks. At present, there is no clinically efficient agent to treat cadmium poisoning due to predominantly intracellular location of cadmium ions. This article gives a brief review of cadmium-induced oxidative stress and its interactions with essential elements zinc and magnesium as relevant mechanisms of cadmium toxicity. It draws on available literature data and our own results, which indicate that dietary supplementation of either essential element has beneficial effect under condition of cadmium exposure. We have also tackled the reasons why magnesium addition prevails over zinc and discussed the protective role of magnesium during cadmium exposure. These findings could help to solve the problem of prophylaxis and therapy of increased cadmium body burden.

KEY WORDS: *carcinogenicity, chelation therapy, dietary supplementation, essential elements*

Detailed historical information on cadmium (Cd) has recently been reviewed by Nordberg (1). A German chemist Friedrich Strohmeyer discovered this metal in 1817. Forty years later, acute gastrointestinal and respiratory symptoms were observed in persons using cadmium carbonate powder as a polishing agent. Increased occupational exposure to Cd was observed after 1912, when the production of nickel-cadmium (Ni-Cd) batteries started in Sweden. Further investigations confirmed the toxic effects of Cd on the lungs, kidneys, and bones. Damage to the lungs in Cd-exposed workers was reported as early as the 1930s, while Nicaud observed osteomalacia and Friberg proteinuria and emphysema in the 1940s (1, 2).

However, it was Itai-itai (ouch-ouch) disease that demonstrated the dangerous dimensions of Cd as an environmental pollutant. It was an endemic bone disease characterised by fractures and severe pain related to exposure to Cd that occurred after World War II in Toyama Prefecture in Japan (1, 3). The clinical symptoms and signs of osteomalacia and osteoporosis, femoral pain, lumbago and skeleton deformations, renal tubular dysfunction, immune deficiencies, apathies, malabsorption, and anaemia were observed mostly in multiparous women living along the contaminated Jinzu River basin. Elevated levels of Cd were found in patients' urine. In 1968, the Japanese government acknowledged that the disease was as an environmental disease related to

Cd-contaminated water released from a mine into the Jinzu River, which was used to irrigate rice fields. The disease was the result of several unfavourable factors: consumption of Cd-contaminated water and rice, low dietary intake of proteins, and essential element deficiencies due to multiple pregnancies. High Cd exposure levels were associated with adverse effects on the skeleton through toxic effects on kidney, and also, as was confirmed later, by direct Cd effects on bone tissue. For the first time, Cd pollution was shown to have severe consequences on human health. Subsequently, interest in Cd, initiated by Friberg's observations of renal damage in occupationally exposed workers, arrived on the scientific scene (2).

The discovery of a Cd-containing protein from horse kidney by Margoshes and Vallee (4) in 1957 marked the beginning of research of this low-molecular weight, cysteine-rich protein named metallothionein by Kägi and Vallee (5). Further studies confirmed the important role of metallothionein in the toxicokinetics and toxicodynamics of Cd and identified the kidney as one of the critical organs of Cd toxicity (6).

Cadmium is classified as a toxic element without any beneficial role in human physiology. Several studies have shown the role of Cd as an essential metal in ruminants (7). It was recently reported that some marine algae contain a form of the enzyme carboanhydrase with cadmium instead of zinc (Zn) in their active sites (8).

Cadmium has also found its place in the rapidly expanding field of nanotechnology, which is therefore likely to become yet another source of its toxicity. Cadmium-containing nanoparticles, known as CdSe or CdTe-core quantum dots, have numerous biomedical applications, especially in the diagnosis of cancer, due to their unique optical and electrical properties. Despite their potential to revolutionise medical therapy, Cd-containing quantum dots are potentially toxic and their use presents substantial risk (9-12).

Over the last 50 years, the awareness and concern about Cd toxicity have resulted in a vast literature on this matter. Cadmium was called "the metal of the 20th century". Future investigations will continue in order to further elucidate its mode of actions and their mechanism(s), identify biomarkers of critical effects, and to develop preventive and therapeutic strategies to decrease Cd body retention (e.g. 13).

This article gives a brief review of Cd research until now, including our own, with a focus on the current significance of cadmium and its modes of action through induction of oxidative stress and interactions with selected essential elements.

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO CADMIUM

Cadmium is ubiquitous environmental and occupational pollutant. Today it is mainly used in the manufacture of nickel–cadmium batteries, pigments, and plastic stabilizers, whereas applications in alloys, solders and electroplating show a decreasing trend. Both natural and anthropogenic activities significantly contribute to environmental quantities of Cd. Natural sources of Cd include volcanic activity, forest fires, and soil particles carried by wind. Anthropogenic sources are copper (Cu) and nickel (Ni) smelting and fossil fuel combustion. Occupational exposure to Cd usually occurs in mines, in the production of batteries and pigments containing Cd, in the production and processing of Cd, its alloys, and compounds, and in recycling electronic waste. The leading producers of this metal, mostly for Ni-Cd batteries, are China, Japan, and Korea. The last few decades have seen a significant drop in the production and use of Cd, especially in the United States and the European Union. However, Cd continues to be a major health problem, mostly because of its long half-life (15 to 20 years) and persistence in the environment and a variety of tissues (14-17).

Air and drinking water Cd levels are not alarming; they keep around 0.04 $\mu g\ m^{-3}$ and below 1 $\mu g\ L^{-1}$, respectively (16). Therefore, air Cd does not significantly contribute to the total dose of Cd absorbed by the body, except in people living near or working in metal industries. Exposure of general population to Cd should be kept as low as possible. The EU has proposed that urinary Cd concentration should be below 0.66 $\mu g\ g^{-1}$ of creatinine (16), which reflects the recent findings on the adverse effects of low-level Cd exposure. In a priority list of hazardous substances established by the US Comprehensive Environmental Response, Compensation, and Liability Act, Cd ranks seventh (17).

Cadmium does not degrade in the environment and can enter the food chain, which steadily increases the risk of human exposure. Cadmium is present in

almost all kinds of food. Its concentration varies greatly with the type of food and the level of contamination. Human activities such as mining, waste incineration, fossil fuel combustion, and application of phosphate fertilisers and sewage sludge that contain Cd significantly contribute to the contamination of soils and consequently, cultivated plants. Wheat and rice, green leafy vegetables, and potatoes contain higher concentration than other foods from plants and account for more than 80 % of Cd intake by food. Cadmium is also present in high concentrations in fish and sea food (molluscs and crustaceans) and also in offal products. Adults across Europe are exposed to Cd levels nearing the tolerable weekly intake (TWI) of 2.5 μg kg^{-1} b. w. Cadmium TWI can also be exceeded in other subgroups such as children, vegetarians, and people who are occupationally exposed or live in polluted areas (16).

Beside food, cigarette smoke is the largest source of non-occupational exposure, because Cd tends to accumulate in tobacco leaves, and between 40 % and 60 % of inhaled Cd can enter blood circulation. Cadmium content in cigarettes may vary with cigarette brand, but the usual content per cigarette ranges between 1 μg and 2 μg. While the average person absorbs around 1 μg of Cd through food per day, smokers that smoke one pack of cigarettes per day can absorb additional 1 μg to 3 μg of Cd and thus heavy smokers have more than double the Cd body content (14, 15).

CADMIUM TOXICITY AND CARCINOGENICITY

The first reported human adverse health effect related to Cd was lung damage in exposed workers. Subsequent studies identified the kidney as the critical organ of Cd toxicity, although Cd also causes adverse effects on the liver, lungs, pancreas, bones, reproductive organs, placenta, and hematopoietic, nervous, and cardiovascular systems (1, 2). In a recent paper Bhattacharyya (18) gave an overview on data that confirm low-level Cd-induced osteotoxicity with decreased bone mineral density and calciotropic hormone levels. The Third US Health and Nutrition Examination Survey (NHANES III) (19), which included 8722 US citizens over the age of 40, showed a significant association between Cd urine content and myocardial infarction. Findings of abnormal fasting glucose and diabetes suggest that Cd may cause pre-diabetes and diabetes mellitus in humans (20). Furthermore, Cd disrupts the endocrine function by binding to cellular steroid receptors and can have oestrogen-like and androgen-like activity (21). Occupational exposure to Cd has been associated with the lung, pancreas, prostate, breast, and kidney cancer (22, 23). The International Agency for Research on Cancer (IARC) and the US National Toxicology Program classified Cd as human carcinogen (category 1) (24, 25). As reviewed by Nawrot et al. (26) this classification is based on evidence of carcinogenicity collected in three lines, that is, epidemiological evidence, *in vivo* and *in vitro* studies. A relationship between Cd exposure and the occurrence of lung cancer was found in exposed workers who had a 20 % higher risk of lung cancer than control workers. A prospective cohort study conducted in an area close to three zinc smelters showed an association between lung cancer incidence and Cd exposure; a twofold increase in 24-h urinary Cd excretion corresponded to a 70 % greater risk of lung cancer. Furthermore, the pulmonary system is a target of Cd-associated carcinogenesis. Lastly, several studies provide evidence that cadmium may have carcinogen potential *in vitro*.

There is no definite evidence that Cd causes prostate cancer and only three out of 11 cohort studies have found a positive association (27). McElroy et al. (22) reported about high risk of breast cancer in women that correlated with the level of exposure. Correlations were also found between Cd levels and age-adjusted prostate and breast cancer incidence in Europe (28).

New methods such as differential gene and protein expression profiling in experimental animals exposed to Cd may help to better understand the mechanisms involved in Cd toxicity and carcinogenesis. This approach can help to develop molecular markers of Cd exposure, toxicity, and carcinogenesis that may be used in epidemiological studies for predicting the incidence of cancer in humans (29).

MECHANISMS INVOLVED IN CADMIUM TOXICITY AND CARCINOGENICITY

Over the last few decades, substantial efforts have been made to clarify the mechanisms of Cd toxicity. However, the precise mechanism(s) underlying

particular toxicity remain unclear. The present knowledge, based primarily on *in vivo* and *in vitro* studies, suggests that Cd may cause numerous cytotoxic and metabolic effects that have not been sufficiently recognised, such as changes in enzyme activity, changes in proteins with sulphydryl groups (thioneins), induction of oxidative stress and apoptosis, changes in the structure and/or function of cell membranes, changes in DNA structure and altered gene expression, inhibition of ATP production in mitochondria, and interaction with Zn, Cu, Ca, Se, and other essential metals (30-32).

Role of cadmium in oxidative stress induction

The first evidence of increased lipid peroxidation (LPO) in mice hepatocytes co-cultured with Cd was given by Müller (33). The author described Cd-induced production of reactive oxygen species (ROS) through interaction with critical subcellular sites such as mitochondria, peroxisomes, and microsomes, that resulted in the generation of free radicals and LPO in subcellular membranous structures. Production of ROS has been reported later in a variety of cell culture systems, as well as in intact animals via all routes of exposure (34-37). We also found early signs of oxidative stress in the liver of mice exposed to a single oral Cd dose (20 mg kg^{-1} b. w. in the form of $CdCl_2$) through increased LPO level, expressed as malondialdehyde (MDA) after 6 h, 12 h, and 24 h (38). Since Cd has no redox activity, it may enhance ROS production by suppressing free-radical scavengers such as glutathione (GSH) and by inhibiting detoxifying enzymes such as superoxide dismutase, catalase, and GSH peroxidase, and/or through other indirect mechanisms (39). The ways in which Cd can induce the formation of reactive species are summarised in Figure 1. Available data confirm that the formation of free radicals such as superoxide ion, hydrogen peroxide, and hydroxyl radicals involves depletion of GSH and changes in the activity of antioxidant enzymes (40). Our recent findings (41) showed that an acute oral Cd dose (20 mg Cd kg^{-1} b. w.) significantly decreased the glutathione (GSH) content in mice liver 4 h, 6 h, and 12 h after Cd administration and increased GSH in the kidney after 12 h, 24 h, and 48 h, but did not cause significant GSH changes in the testis. A two-week oral Cd exposure (at dose of 10 mg kg^{-1} b. w. of Cd given as aqueous solution of $CdCl_2$) lowered renal levels and increased liver and testicular levels of GSH. These results, together with related findings of other authors, show that the effect of Cd on GSH tissue levels varies with animal species, dose, route, and duration of exposure. In general, acute exposure to metals decreases GSH levels due to the formation of metal-GSH complexes and/or consumption by the GSH-peroxidase under oxidative stress induced by metals.

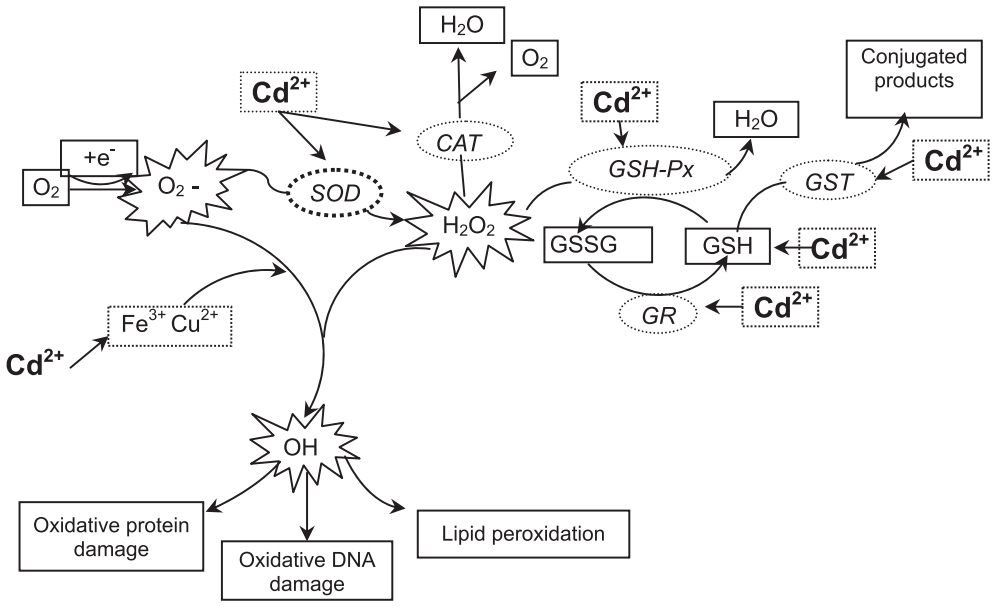

Figure 1 *Pathways of Cd-induced generation of reactive oxygen species (adapted from ref. 39 by Danijela Đukić-Ćosić). Cadmium impairs enzyme activity of antioxidative defence system (superoxide dismutase, SOD; catalase, CAT; glutathione peroxidase, GSH-Px; glutathione-S-transferase, GST; gluathione reductase, GR) and of the non-enzymatic component glutathione, GSSG and GSH.*
Cadmium also elevates the levels of Fenton metals (Fe^{3+}, Cu^{2+}), which can break down hydrogen peroxide, H_2O_2 to a reactive hydroxyl radical, OH.

Casalino et al. (42) have proposed yet another mechanism of Cd-induced ROS production via iron (Fe). Cadmium may displace Fe from various cytoplasmic and membrane proteins and consequently, increased concentration of ionic Fe stimulates ROS production in tissue. This is in agreement with our recent findings, which clearly show that acute and subacute Cd exposures change Fe content in the liver of mice (38). The results of this study also indicate that Cd affects MDA levels in a time-dependent manner. The observed MDA levels positively correlated with Fe in the liver. Oral exposure to a single dose of Cd (20 mg kg^{-1} b. w.) significantly increased LPO in the liver at 6 h, 12 h, and 24 h, and liver Fe after 4 h and 6 h up to 110 % of control level. However, in mice orally exposed to Cd for two weeks (10 mg kg^{-1} b. w. in form of $CdCl_2$ in aqueous solution), we found liver Fe reduced by 80 % and MDA by 74 %.

There are several other proposed mechanisms of Cd-induced oxidative stress. One of these is Cd-induced inflammation in the liver. Kupffer cells are activated in response to Cd overload and produce inflammatory mediators such as IL-1β, TNF-α, IL-6, and IL-8, which in turn stimulate generation of free radicals in the liver (43). It has also been suggested that mitochondria are an important target of Cd toxicity (44).

When it comes to ROS production, the results of long-term exposure to low levels of Cd depend on experimental conditions such as dose, time intervals of oxidative stress evaluation, and animal species studied. It seems that ROS production has an important role in chronic Cd nephrotoxicity (45), immunotoxicity (46), and carcinogenesis (47). On the other hand, chronic exposure to Cd often elevates tissue GSH, without elevating tissue LPO levels (37, 45). This is confirmed by our own results (38), which showed initial increase in liver LPO and Fe levels 24 h after a single oral dose, which dropped after repeated Cd dosing. Prolonged Cd exposure through drinking water also caused a two-phase ROS response. At the beginning, ROS production rose, only to drop back to normal after eight weeks of exposure (48). It has been shown that ROS production does not play an essential role in chronic Cd-induced malignant transformation in rat liver cells (49).

Interactions between cadmium and essential elements

It is well known that Cd interferes with the biokinetics and biological roles of many essential metals and metalloids such calcium (Ca), magnesium (Mg), sodium (Na), potassium (K), Zn, Cu, Fe, manganese (Mn), selenium (Se), molybdenum (Mo), trivalent chromium (Cr), cobalt (Co), boron (B), and other (30-32). However, the exact mechanisms involved in these interactions have not been entirely identified.

Cadmium and Zn interactions probably are one of the most recognised metal-metal interactions due to increasing environmental Cd exposure of the general population and concomitant widespread Zn deficiency in the world (14-17, 50). Since Zn is a co-factor in numerous enzymes and regulatory proteins, including the enzymes of DNA and RNA synthesis and repair, Cd-induced disturbances in Zn homeostasis may have serious consequences on cell growth, development, and their functions. Because these two transitional metals are similar (both belong to the group IIb of the periodic table and form tetrahedral complexes) they compete for the same binding sites and/or ligands in biological systems.

A number of studies including our own (51-55) have shown that Cd disrupts Zn homeostasis. In turn, certain Cd-induced toxic effects, such as adverse reproductive and perinatal effects, may be amplified when Zn is depleted. Osman et al. (56) reported that multiparae, cigarette smokers in particular, run the highest risk of prenatal Cd toxic effects, which are associated with low Zn concentrations in serum, placenta, and cord blood. Exposure of rats to Cd lowered Zn levels in foetal tissues, accompanied by reduction of Zn metalloenzyme activities in both maternal and foetal tissues, which may be responsible for adverse reproductive outcomes (57). Our recent study on rabbits (58) has shown that prolonged oral exposure to Cd (10 mg kg^{-1} b. w. per day during four weeks) significantly lowered Zn in blood and nine organs.

Interactions between Cd and Mg have been less investigated than interactions with other essential metals, regardless of the fact that Mg has an outstanding physiological and biochemical role. Literature data and our own results suggest that Cd interferes with Mg absorption in the gastrointestinal tract and affects its homeostasis as well. We found altered Mg content in the organs of rabbits after prolonged Cd exposure (58, 59). Our new and yet unpublished investigations carried out on mice have confirmed these negative effects of Cd exposure (both by single oral dose to 20 mg kg^{-1} b. w. and 10 mg kg^{-1} b.w. per day during two weeks) on Fe, Zn, Cu, and Mg tissue levels.

More than thirty years ago, Smetana et al. (60) suggested that interaction between Cd and Mg might play a crucial role in the pathogenesis of idiopathic dilated cardiomyopathy. In the blood and urine of these patients Cd was increased, Mg decreased, whereas other metals (Pb, Zn, Cu, and Fe) were within reference range. While trying to determine the lowest Cd level in urine that is still associated with tubular dysfunction in Japanese women, Ezaki et al. (61) discovered that increased urine Cd levels were accompanied by increased excretion of Mg.

In spite of significant improvements in occupational safety achieved in the last fifty years, recent literature data indicate that Cd exposure levels in certain occupational settings still remain as high as those reported in the factories of developed countries before the 1950s. In our recent study (62) of Ni-Cd factory workers in Serbia we determined blood and urine Cd levels to see if there were any Cd-induced effects on the renal function and concentrations of Zn, Cu Mg and Fe in blood and urine. Although we expected them to be high, Cd levels kept within the range proposed by the World Health Organization (63) for occupationally exposed subjects (10 μg L^{-1} for blood and 10 μg g^{-1} of creatinine in urine). Altered values of β_2-microglobulin indicated disturbed renal function in only a few workers. We also found significantly lower concentrations of Mg in blood and of Zn in blood and urine.

Taken together, these results and similar reports in the field show that Cd interacts with several essential elements. In order to prevent adverse health effects, exposure to Cd should be as low as possible and exposed persons should include essential nutrient supplementation in everyday diet.

Interactions between essential elements and cadmium

Zinc and cadmium interaction

The antagonism between Cd and certain essential elements encouraged investigators to evaluate whether micronutrients such as Zn may influence Cd toxicity. Pařizek (64) published first data on beneficial effects of Zn supplementation against Cd toxicity as early as 1957. Later research of acute Cd exposure showed that Zn inhibited Cd transport along the terminal nephron segments in rats and *vice versa* (65). Jacquillet et al. (66) confirmed that Zn addition during Cd exposure prevented metal-induced changes in rat renal functions. Dietary Zn supplementation may also prevent Cd-induced disorders in bone turnover. Brzóska et al. (67) reported that increased Zn intake during moderate or relatively high chronic Cd exposure can, at least partly, prevent disorders in bone metabolism.

Experimental data show that Zn can have an important impact on Cd-induced carcinogenesis as well. Waalkes et al. (68) suggested that excess Zn intake affected Cd-induced prostate cancer by preventing testicular toxicity and maintaining testosterone production. Hu et al. (69) explored possible mechanisms responsible for Cd-induced reproductive toxicity and prostate cancer in relation to Zn. They monitored the expression of metallothionein genes, proto-oncogenes and tumour-suppressor gene p53 in rat prostate and testis, together with changes of testosterone level in serum. They showed that Cd-induced toxicity and the effects of Zn were complex. Although both Cd and Zn reduced testosterone, the initiation of prostate cancer is rather related to Cd-induced altered gene expression.

In a recent investigation (70), we exposed rabbits to Cd (as $CdCl_2$ in aqueous solution at oral dose of 10 mg kg^{-1} b. w. of Cd per day) for four weeks and found that concomitant oral supplementation with Zn (as $ZnSO_4$ in aqueous solution at dose of 20 mg kg^{-1} b. w. of Zn per day, given 1 h following Cd administration) reduced concentrations of Cd in blood and kidney (by 60 %) and to a lesser extent in the spleen, brain, and bone, in comparison to rabbits exposed to Cd only. The decrease in the Cd levels in analysed tissues was most probably due to the interaction between Zn and Cd in the intestinal lumen, where higher Zn content lowered gastrointestinal absorption of Cd. Cadmium uptake occurs predominantly through Zn-associated co-transport, as both ions compete for common binding sites and for membrane carriers such as divalent metal transporter-1 and luminal Zn transporter-1 (71). Our results (70) also showed that Zn decreased renal Cd, but did not reduce hepatic Cd, probably due to Zn-induced synthesis of metallothionein in the liver, which caused Cd accumulation in the liver and delayed its redistribution to the kidney. Zinc-associated lower Cd levels in spleen may be owed to the fact that this organ is richly vascularised and these values actually reflect blood Cd levels. Lower Cd brain levels after excessive intake of Zn could be explained by the ability of Zn to induce metallothionein synthesis, and the Cd-metallothionein complex can hardly cross the blood-brain barrier. Recent investigations of the probable

protective mechanisms of Zn in Cd-exposed rats showed increased Cd levels in the kidney and suggested other protective mechanism of Zn action than MT synthesis, such as direct antioxidant action of Zn and Zn-improved activity of antioxidant enzymes (72).

Magnesium and cadmium interaction

Limited experimental data point to beneficial effects of Mg against Cd toxicity. Boujelben et al. (73) showed that Mg supplementation could reduce both organ Cd accumulation and Cd-related LPO. The authors found that parenteral Mg supplementation (in form of sulphate) was associated with a dose-dependent reduction in Cd levels in rat kidney, liver, and testis and lowered Cd-induced LPO in the liver and kidney. In the testis, the protective effect of Mg was present only during the early phase of Cd-exposure.

We investigated the effect of supplemental magnesium in mice exposed to Cd (74). While acute oral Cd exposure (20 mg kg^{-1} b. w.) resulted in a significant renal Cd increase, pretreatment with Mg (40 mg kg^{-1} b. w) efficiently lowered kidney Cd levels 4 h and 6 h after Cd exposure. Similarly, the Cd content in the kidney was also elevated following two-week Cd exposure (10 mg kg^{-1} b. w. per os), and the effect was diminished by about 30 % in mice pretreated with Mg (20 mg kg^{-1} b. w. per day). These results provide evidence that Mg has the ability to protect the kidney from Cd accumulation and point to the beneficial effects of Mg supplementation against Cd-altered renal Cu and Zn levels (74).

Our further investigation (41) showed that Mg pretreatment significantly lowered Cd content not only in the kidney (~30 %), but also in the lungs (50 %), spleen (~30 %), and testis (~30 %), following two-week Cd exposure.

Results of our investigation on rabbits (70) exposed orally to Cd (as aqueous solution of $CdCl_2$ at dose of 10 mg kg^{-1} b. w. per day) for four weeks also showed that concomitant Mg supplementation (40 mg kg^{-1} b. w. as an aqueous solution of $Mg(CH_2COO)_2$ per day given 1 h after Cd administration) had the beneficial effects against tissue accumulation of Cd. Excessive intake of Mg reduced blood, kidney, spleen, and bone Cd levels for about 30 % in respect to rabbits given only Cd. However, we did not observe any relevant changes in the lungs, heart, liver, pancreas, muscle, and brain. This suggests that Mg modifies Cd absorption in the gastrointestinal system by affecting the intercellular leak of Cd from intestinal lumen to portal blood and thus reduces peripheral blood Cd. The effect of Mg supplementation on renal Cd retention could be explained by Cd-Mg competition during reabsorption. Furthermore, increased Mg in the lumen of the distal nephron could disable Cd uptake by intercellular transport and promote Cd elimination via urine.

THERAPY OF CADMIUM POISONING

No effective therapy of Cd poisoning has yet been developed, and currently it only addresses the symptoms (14). The most common agents, which have been used against heavy metal poisoning since World War 2 are chelators, starting with British Anti-Lewisite (BAL). After the war, calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$), deferoxamine, and D-penicillamine were introduced in clinical practice (75). However, none of the available chelating drugs is effective against poisoning with Cd because it quickly enters the tissue and binds to metallothioneins (14, 75). Some chelating agents such as polyaminocarboxylic acids [e. g. $CaNa_2EDTA$, calcium trisodium diethylenetriaminepentaacetate ($CaNa_3DTPA$), and zinc trisodium diethylenetriaminepentaacetate ($ZnNa_3DTPA$)], carbodithioates, deferoxamine (DFO), *N*-acetylcysteine (NAC), and 2,3-dimercaptosuccinic acid and its esters have shown some effectiveness in experimental animals when applied very soon after Cd exposure (75).

Literature data indicate the protective role of Zn supplementation against Cd toxicity, possibly because it stimulates metallothionein synthesis and competes with Cd for enzyme-binding sites (14, 67, 76-78). In addition, some studies have shown favourable effects of pretreatment with other essential elements on Cd toxicity (79, 80). Supplementation with minerals has not yet been approved for clinical use, since it is still not clear whether it is effective in subjects with adequate essential element intake, or only in Zn- and/or Ca-deficient individuals Similarly, the role of supplementation with antioxidants, such as vitamins A, C, or E, has been investigated in experimental settings in order to find an effective way to counter Cd-induced oxidative stress in tissue (14).

In our recent study of Cd in exposed rabbits (81), we determined the effects of increased oral intake

of Zn, Cu or Mg on the kinetics of Cd in various tissues to assess whether treatment with one of these bioelements could be used in prophylaxis and/or therapy of Cd poisoning. Rabbits were administered Cd by gastric tube (as aqueous solution of $CdCl_2$ at dose of 10 mg kg^{-1} b. w. per day) for four weeks, and three groups were supplemented oral Zn, Cu, or Mg [as aqueous solutions at doses of 20 mg kg^{-1} b. w. of Zn in the form of $ZnSO_4$;10 mg kg^{-1} b. w. of Cu in the form of $CuSO_4$; or 40 mg kg^{-1} b. w. of Mg in the form of $Mg(CH_3COO)_2$] one hour after Cd exposure. Concentrations of Cd and essential elements were determined in blood and urine samples collected at different time intervals during the experiment and in nine organs (brain, heart, lungs, kidney, liver, spleen, pancreas, skeletal muscle, and bone) dissected at the end of experiment. Zinc supplementation was associated with reduced blood Cd throughout the experiment. Significant decreases were also determined in the kidney, brain, spleen, and bone. Similarly, Mg supplementation significantly reduced Cd in blood, kidney, spleen, and bone, without any significant changes in urine Cd. Contrary to Zn and Mg, Cu supplementation did not reduce Cd levels in blood, heart, and liver. These results have confirmed the antagonism between Cd and Mg as well as between Cd and Zn, which is similar to our findings on the antagonism between Pb and Mg in experimental rabbits (82-86).

The effects of either Zn or Mg supplementation on Cd concentration and distribution in various tissues show similar beneficial effects on Cd body burden reduction in exposed rabbits. Although we found that Zn more efficiently reduced Cd tissue levels, especially in the kidney, we propose Mg as a dietary supplement of choice for reduction of Cd body burden, as the addition of Mg did not disturb either Zn or Cu levels. In turn, excessive Zn intake in our studies reduced Mg levels in blood and most of the investigated organs and increased its elimination via urine (58). Magnesium has a wide therapeutic range, and therefore further investigations are needed to justify its efficiency as a therapeutic agent against toxic metals, Cd in particular.

CONCLUDING REMARKS AND PROSPECTS

Cadmium is an occupational and environmental pollutant whose toxicity was eagerly investigated during the last decades. The pervasive nature of Cd in the environment and in biological tissues may have serious consequences, especially with respect to the role of Cd as a human carcinogen. Although the toxic effects of Cd are well known, the specific mechanisms by which it produces its adverse effects have yet to be fully investigated. Cadmium can cause oxidative stress, which may lead to cytotoxic and carcinogenic effects in target organs, and deeper insight into these mechanisms can give proper explanations to protect exposed population groups. However, there are great differences between *in vivo* and *in vitro* effects of Cd that still need to be addressed in research.

Literature data show that Cd affects the homeostasis of essential metals at the cell level. This review has focused on results, including our own, showing interactions between Cd and bioelements Mg and Zn. In general, exposure to Cd reduces the levels of essential elements, which may have adverse health effects. On the other hand, Mg or Zn supplementation has a beneficial role in reducing Cd body burden and could be used for prevention and/or therapy. Years of our investigations in the field have confirmed the advantage of Mg over Zn supplementation. New research should look deeper into these complex interactions, as they go far beyond mere metal substitutions and are mediated in part by redox-sensitive systems acting at the transcriptional and transductional levels. A clearer insight into cation transporters and their specificity, cation effects on cell membrane transport, intracellular stores of Cd, and molecular regulation of homeostasis of essential metals might help to explain interactions between Cd and essential metals.

Future research should fill in the lacking information to be used for environmental and human risk assessment. This information might be obtained by developing novel biomarkers for early detection of Cd-induced toxicity in exposed populations, subgroups in particular. Analytical methods should be improved by the -*omics* biomarkers and sophisticated biomarkers that keep pace with new Cd-exposure scenarios, such as exposures to Cd-based nanoparticles.

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Sažetak

JOŠ O TOKSIČNOSTI KADMIJA - S POSEBNIM OSVRTOM NA NASTANAK OKSIDACIJSKOGA STRESA I NA INTERAKCIJE S CINKOM I MAGNEZIJEM

Iako je otkriven tek 1817. godine, kadmij je trenutačno jedan od najvažnijih onečišćivača životne i radne sredine. Štetno djeluje na bubrege, živčani sustav, kosti, reproduktivni sistem, a ima i genotoksične i karcinogene efekte. Nužna su dalja istraživanja vezana za mehanizme njegove toksičnosti, biomarkere efekata, kao i načine smanjenja rizika za zdravlje. Osim toga, do danas nije otkriven agens efikasan u terapiji trovanja kadmijem s obzirom na to da je kadmij intracelularni kation. U ovom radu dan je sažet pregled važnih mehanizama toksičnosti kadmija, kao što su nastanak oksidativnog stresa i interakcije s esencijalnim elementima, cinkom i magnezijem, na osnovi dostupnih literaturnih podataka, kao i naših ispitivanja koja upućuju na to da povećani unos navedenih esencijalnih elemenata pokazuje pozitivne efekte pri ekspoziciji kadmiju. Obrazložena je prednost suplementacije magnezijem pred suplementacijom cinkom i razmatrana preventivna uloga magnezija pri intoksikaciji kadmijem. Ovi su rezultati doprinos rješavanju problema profilakse i terapije trovanja kadmijem.

KLJUČNE RIJEČI: *esencijalni elementi, karcinogenost, kelatna terapija, suplementacija*

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