Antagonism between cadmium and magnesium: a possible role of magnesium in therapy of cadmium intoxication

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Abstract. One of the important mechanisms of cadmium (Cd) toxicity is its interactions with bioelements, including magnesium (Mg). Exposure to Cd leads to disturbances in Mg metabolism in the organism, while Mg supplementation has an adverse effect on Cd absorption, accumulation and toxicity. According to the available results, which indicate a protective role of Mg against Cd toxicity, it remains to be seen whether magnesium may influence the important unsolved problem of Cd intoxication therapy. In this review, the interactions between the toxic metal Cd and the bioelement Mg are discussed on the basis of the available literature and our own results. We discuss these interactions mainly based on experimental data because data from human studies are scarce.

Key words: cadmium, magnesium, interactions, toxicology

Besides being an important occupational toxicant, cadmium (Cd) is widespread in our environment because of contamination through anthropogenic activities and it poses major environmental health problems in modern society, with potentially dangerous bioaccumulation through the food chain. This toxic metal is listed by the US Environmental Protection Agency as one of 126 priority pollutants [1] and currently ranks 7th on ATSDR Priority List of Hazardous Substances [2].

Today, the main uses of Cd are for nickel (Ni)-Cd battery manufacture, pigments, and plastic stabilizers, whereas applications in alloys, solders and electroplating show a decreasing trend. Other sources of concern are phosphate fertilizers, which may contain high concentrations of Cd, and the application of contaminated sewage sludge as a soil amendment, waste incineration and the recycling of electronic waste. In 2004, worldwide production was about 17,800 tons/year. Its usage in developed countries has, however, begun to decline because of its toxicity. The general population can be exposed to unacceptably high concentrations of Cd through contaminated water, air and food. Smoking is another source of environmental exposure to Cd since tobacco leaves accumulate this metal.

Damage to the lung in Cd-exposed workers was the first human health effect related to Cd in a report published as long ago as the 1930’s [3], but nowadays it is known that Cd adversely affects a wide variety of human organs, primarily causing kidney damage. Cadmium can also have adverse health effects on liver, bones, testes and the hematopoietic, the nervous and the cardiovascular systems, some of which may occur over extended periods and may depend on the route of exposure [4]. Cd is a potent human carcinogen and occupational exposure to it has been associated with cancers of the lung, the prostate, the pancreas and the kidney. Because of its characteristics as a lung carcinogen, Cd has been classified as a category 1 carcinogen.
(human carcinogen) by the International Agency for Research on Cancer and the National Toxicology Program of the USA [5, 6].

Recent data confirm the negative osteotoxic effects of low-level Cd exposure, e.g. on bone mineral density and calcitropic hormones [7, 8]. Environmental exposure to Cd appears to be associated with renal cancer [9], as well as breast cancer [10]. A recent US study showed an association between Cd content in urine and myocardial infarction [11] and both impaired fasting glucose and diabetes, suggesting that Cd may be a cause of prediabetes and diabetes mellitus in humans [12, 13].

Numerous investigations have been reported on Cd toxicity, although the mechanisms of its deleterious effects, particularly the role of interactions with bioelements, are still not clear.

Present knowledge indicates that Cd may cause numerous cytotoxic and metabolic effects that have not been sufficiently recognized, such as alterations of various enzyme activities [14-16], changes in proteins with sulphhydryl groups (thioneins) [17], induction of oxidative stress [18-21] and apoptosis [22], changes in the structure/function of the cell membrane [23, 24], changes in DNA structure and altered gene expression [25, 26], inhibition of ATP production in mitochondria [27], interaction with Zn, Cu, Ca, Se and other essential metals [28, 29].

Among the most studied are cadmium interactions with Zn and Cu, then Ca and Fe, and there are also data on interactions between Cd and Se, Mg, Mn, Na, K, Mo, B, Co, Cr etc. [30]. This review is focused on the interactions between Cd and Mg.

Therapy of Cd poisoning has not been resolved yet, since the application of known chelate agents does not produce satisfactory results [31]. The standard therapy of heavy metal poisoning relies predominantly on usage of chelating agents. Chelating agents have been used as antidotes for metal intoxication since the Second World War, British Anti-Lewisite (BAL) being one of the first applied chelators. After the war, calcium disodium ethylenediaminetetraacetate (CaNa2EDTA), deferoxamine, and D-penicillamine were introduced in clinical practice. To date, many chelating agents have been synthesized in order to find those effective in preventing heavy metal toxicity. While treatment with chelating agents is undoubtedly effective, it has several drawbacks: non-selectivity, side effects, mode of administration and it has not been accepted as the ideal. They are usually given in a hospital setting even when a patient is asymptomatic, making treatment costly. Furthermore, there are unsolved problems with chelation of some toxic metals such as cadmium, where such a treatment, unfortunately, does not appear useful. Therefore, in spite of the number of chelating agents currently used as antidotes in metal poisoning, further investigations of new therapeutic protocols for metal toxicity are necessary.

Our pioneer investigations on the interactions between toxic metals and bioelements started in the sixties, and were focused on lead (Pb) and its effect on bioelements [32-34]. This long-term investigation showed that high Mg intake had a beneficial effect against Pb intoxication, if Mg was given after prolonged Pb intoxication, or simultaneously with Pb, thus, the therapeutic and prophylactic effect of Mg was confirmed experimentally [35-40]. We also investigated the interactions between Cd and Mg intoxication in the hope that Mg supplementation would have a beneficial effect on Cd toxicity. In this review, the results of our experiments will be presented briefly, simultaneously with other literature data dealing with interactions between Cd and Mg. The main idea was to discuss all available findings and try to find out whether Mg supplementation could influence the therapy of Cd intoxication.

### The effect of Cd intoxication on Mg status

Having in mind the toxicological importance of Cd on one side and the physiological and biochemical importance of Mg on the other, it is hard to believe that interactions between these two metals are less investigated than interactions between Cd and other bioelements such as Zn, Cu, Ca and Fe. Literature data indicate that Cd induces inhibition of Mg absorption in the gastrointestinal tract, and influences the homeostasis of this essential element. Our previous investigations carried out on rabbits showed that prolonged Cd intoxication induces a decrease of blood Mg concentration, and enhanced elimination of Mg via urine. Mg content in the organs of experimental animals was altered: Mg content was elevated in the liver, reduced in muscle, while no significant changes were shown in brain, heart, lungs, kidney and bone [41-43]. Speich et al. [44] also found an increase of Mg in the lungs, liver, adrenal gland and spleen in rabbits and gave the explanation that this rise of Mg in the tissues with high metabolic activity may have served to combat the harmful effects of Cd. Other authors [45] investigated the effects of Cd administration on the endogenous metal balance in rats and concluded that the level of Mg in kidney was increased for all exposure routes (through diet, oral or intravenous administration), while that in liver was increased only in the intravenously injected groups. Furthermore, the Mg kinetics
were dose-dependant. Thus, Noël et al. [46] reported a rise of Mg in liver of rats subchronically exposed to 10 mg CdCl₂/kg, while treatment with higher doses (50 and 200 mg) resulted in a significant decrease of Mg concentration in the liver. Recent investigations confirmed a significant increase of Mg content in liver, kidney and testes in rats injected with 2.5 mg CdCl₂/kg for 10 days [47]. Nevertheless, Durlach discussed in his book that chronic poisoning with Cd causes secondary Mg deficiency [48].

Thirty years ago, Smetana et al. [49] indicated that interactions between Cd and Mg could be one of the crucial factors in the pathogenesis of idiopathic dilated cardiomyopathy. A significant increase of Cd and a decrease of Mg were observed in the blood and urine of patients with this pathology, whereas the other investigated metals (Pb, Zn, Cu and Fe) were within control levels. In Japan, investigations were performed with the aim of determining the lowest Cd content in urine which could cause tubular dysfunction in women [50]. It was established that an increase of Cd levels was not only accompanied by an increased urine level of cadmium, but also by increased excretion of magnesium. Recently, we investigated occupational exposure to cadmium and its effect on bioelements. The results indicated that Cd exposure to workers in Ni-Cd battery production resulted in blood Mg reduction [51].

Basic mechanisms of interactions between cadmium and magnesium

Cd and essential metals can interact by influencing each other’s rates of absorption, retention, distribution and bioavailability in the body. This is mainly because of their competition for the same binding sites, especially –SH groups, in various enzymes and other metalloproteins such as metallothionein (MT) [29]. Lower blood Mg levels, generally thought to be a result of Cd exposure, could be explained by an increased Cd level in the gut, induced by mucociliar transfer, by bile elimination or by excretion of Cd through the intestine walls [4], which in turn may cause an inhibition of Mg absorption in gut, thus leading to a decrease of blood Mg. The other possibility is that Mg from blood moves to target organs and tissues as a consequence of organism system defense against Cd toxicity. Furthermore, it has to be kept in mind that there are no known specific uptake mechanisms for the nonessential toxic metals, Cd being one of them; thus, the accumulation of this metal probably occurs through processes that exist for the essential metals, at least partly for Mg. As a result of competition between Cd as a toxic metal and Mg, a disruption of Mg intracellular balance occurs, resulting in toxic responses.

Quamme et al. designed a series of experiments to investigate the interaction of Cd with the Mg entry pathway [52-54] and indicated that Cd may cross the plasma membrane through the Mg entry pathway. This may have significant impacts on the action of Cd in various cell types possessing these pathways [55].

Apart from the fact that Mg is the second most abundant element in cellular systems and of great physiological importance, only a few Mg transporters have been identified in mammalian cells until now. Furthermore, none of the transporting has been associated with Cd-Mg interactions. Recently, Lévesque et al. [56] investigated Cd uptake and cytotoxicity in human osteoblast-like MG-63 cells, as little information is available about the direct effects of Cd on osteoblastic cells. The cellular accumulation and cytotoxicity of Cd were reduced by 2-APB, a known inhibitor of the Mg and Ca channel TRPM7 and were increased in the absence of extracellular Mg. The inhibition of Cd uptake by Mg and Ca was not additive, suggesting that each ion inhibits the same uptake mechanism. The authors concluded that Cd uptake in human osteoblastic cells occurs, at least in part, through Ca- and Mg-inhibitable transport mechanisms, which may involve channels of the TRPM family. Contrary to these channels, the newly identified MagT channels are Mg-specific transporters, but in vitro investigations did not confirm their involvement in transport mechanisms for Cd [52, 53].

The effect of Mg supplementation on Cd metabolism

Since it was obvious that Cd exposure induces a dis-balance of Mg, investigations were conducted in order to assess the effect of Mg supplementation on the Cd body burden.

The effect of Mg on Cd levels in different tissues

We investigated the effect of supplemental Mg in mice intoxicated with Cd. Acute oral intoxication with 20 mg Cd/kg b.wt resulted in a significant increase of Cd content in kidney. The protective effect of Mg, decreasing the renal uptake of Cd, was observed 4 and 6 h after the intoxication. After 2 wks of Cd intoxication with a dose of 10 mg Cd/kg b.wt, the Cd content in the kidney was also significantly elevated. This effect was
diminished in the group of animals pretreated with 20 mg Mg/kg b.wt /day. Cd content in the kidney was approx. 30% lower in mice given Mg [57]. Data acquired from this experiment provide evidence that Mg has a significant ability to protect the kidney against the accumulation and toxicity of Cd. Our previous investigations also showed that Mg pretreatment significantly lowered Cd content in the lungs, spleen and testis in mice after 2 weeks, in the case of sub-acute Cd intoxication. The decrease was about 30% in kidney, spleen and testis, whereas it reached 50% in the lungs [58].

Recently we investigated the effects of Mg supplementation on Cd content in rabbits exposed to prolonged Cd intoxication [59]. Experiments were performed on rabbits given 10 mg Cd/kg b.wt as an aqueous solution of CdCl₂ orally every day for four weeks and rabbits exposed to the same dose of Cd and, 1 h later, supplemented orally with 40 mg Mg/kg b.wt as an aqueous solution of Mg-acetate. The results of this study indicate that excessive oral intake of Mg reduces Cd blood levels in animals intoxicated with Cd. The beneficial effects of Mg content were also observed in the kidney, spleen and bone, where a significant decrease of Cd was found as compared to animals given only Cd, although the decrease in urine Cd levels was not significant. The authors proposed two possible explanations for the Cd reduction in the blood. The first one is that Mg modifies Cd absorption in the gastrointestinal tract (GIT) by its influence on Cd intercellular leaking from the intestinal lumen to portal blood. The second one is that Mg modifies the Cd distribution in the organism, although this hypothesis is not supported by the results obtained. Mg supplementation resulted in a 30% decrease of Cd in the kidney. This finding is of special importance since the kidney is a critical organ in Cd toxicity and is the main organ responsible for the regulation of Mg. As reported by Boujelben et al. [47], injection of Mg lowered the Cd content in the kidney, liver and testes in rats injected 2.5 mg Cd/kg b.wt/day for 10 days. Different doses of Mg were used, and the Cd reduction was dose-dependent. In contrast to these findings, some authors found no decrease of Cd in the kidneys of rats fed diet with Mg during Cd intoxication [60]. This could be explained by the significantly lower dose of Mg used in these investigations. A hepatoprotective potential of Ca and Mg against Cd and Pb in a rat model was recently reported, based on the measured liver-specific enzyme activities, total protein, albumin and immunoglobulin concentrations, as well as on histopathological examination of the liver [61].

**Mg and Cd teratogenicity and embryotoxicity**

One of the questions concerning antagonism between Cd and Mg is whether Mg treatment can influence teratogenic and embryotoxic effects of Cd. Ultrastructural studies performed at the beginning of the nineties on an isolated human amnion membrane [62] showed that Cd decreased the intercellular space volume, increased the microvillus space volume and thus increased the cellular route in the fetus-to-mother direction. The addition of Mg antagonized the effects of Cd on the intercellular space, and the authors concluded that Mg is a competitive inhibitor of cadmium. Experiments performed on frog embryos [63] have shown that Mg supplementation significantly reduced the incidence and severity of the teratogenic and embryotoxic effects of Ni, Co, Zn and Cd. To explain these findings, Luo et al. [63] postulated that Mg competes with the other divalent metal ions for a carrier mechanism involved in metal absorption or cellular uptake, or for binding to critical molecular targets. This was confirmed by Boga et al. [64] who also used frog embryos and concluded that Zn and Mg can suppress the teratogenic and toxic effects of xenobiotic cations such as Cd, Ni and Co. The research was also conducted to investigate the toxic effects of cadmium administered on female albino mice and their offspring during gestation and to investigate the potential protective effect of either Mg or vitamin E [65]. This study demonstrated that Mg is more potent than vitamin E in protecting female mice and their offspring from Cd-provoked defects. Mg administration completely prevented embryonic, haematological, hepatological and renal toxicities, whereas vitamin E supplementation caused only moderate improvements in these defects. As the concentration of Cd was still high in the bodies of the newborns, the authors concluded that the protective action of Mg may be due to either the antagonistic effect of Mg and/or the stimulatory effect of Mg in producing de novo GSH.

**Mg and Cd carcinogenicity**

Cd has been classified as a category 1 carcinogen since 1993, but the mechanisms by which Cd induces cancer are poorly understood. Two mechanisms seem to a play predominant role at the molecular level: inhibition of DNA repair and induction of reactive oxygen species [66], although, just recently, Joseph [67] proposed that the major mechanisms involved in Cd carcinogenesis can be broadly categorized into four groups, aberrant
gene expression, inhibition of DNA damage repair, inhibition of apoptosis and induction of oxidative stress. There is increasing evidence that Cd can inactivate several DNA repair enzymes. Thus, investigations on human cells exposed to sub-lethal concentrations of Cd lead to a time- and concentration-dependant decrease of the DNA glycosylase activity [68]. Furthermore, the results obtained on cadmium exposed human endothelial cell lines suggest that the toxicity of Cd compounds may be explained by the propagation of persistent DNA double strand breaks, which was associated with an over-activation of the double-strand break repair protein MRE11, that may favour genomic instability [69]. One of the major questions facing toxicologists is whether one can control Cd carcinogenicity and furthermore if Mg could be of some help. Among the first studies concerning the interactions of Cd and Mg was the one investigating the effects of Ca- and Mg-acetates on the carcinogenicity of cadmium in rats [70]. The results clearly demonstrated that the development of tumors at the site of a s.c. Cd injection can be prevented by simultaneous injections of Mg acetate at the same place, whereas the injection of Ca did not produce such protective effects. Dietary administration of either Ca or Mg was completely ineffective in preventing Cd-induced sarcomas. There is an evident association between Mg and the development of lymphoid malignancies. Waalkes and Poirier [71] showed that Mg is a competitive antagonist of Cd binding to high affinity sites, in double-stranded calf thymus DNA. Only two years later Kasprzak and Waalkes [72] reviewed the roles of several metals, among them Mg, and their effects on carcinogenesis. They indicated that Mg and Zn tend to inhibit carcinogenesis and that a deficiency of Mg increased the incidence of neoplasia in both humans and animals. Littlefield et al. [73] investigated the protective effect of Mg on DNA strand breaks induced by Ni and Cd, using human and rodent lymphocytes. Based on the results of this study, Mg has little or no direct influence on the occurrence of DNA damage from nickel since the toxicity of Ni appears to manifest itself in other sites than DNA, whereas Cd results in DNA damage, which was significantly reduced by Mg. The protective effect of Mg against Pb and Cd was also investigated in sheep lymphocytes: Cd inhibited repair of DNA damage caused by UV irradiation in sheep lymphocytes but this effect was markedly mitigated by the presence of Mg. The presence of Pb did not appear to directly affect the DNA, contrary to Cd. Despite UV irradiation, the DNA damage was enhanced by Cd but reduced in the presence of Mg [74]. However, there are opposite results, which indicate that application of Mg cannot prevent DNA repair inhibition by Cd, although it can completely prevent the same effects of Ni, which is also a carcinogenic metal [75].

Although all these investigations confirm the possibly important role of Mg in preventing Cd induced carcinogenesis; a number of questions are left unanswered. The role of Mg per se in carcinogenesis is still not clear. Mg stabilizes the DNA structures at physiological levels, whereas it destabilizes them at low or higher concentrations. Mg supplements are therefore necessary in cases of Mg-deficiency in order to avoid possible dysfunctions or diseases [76].

Mg against Cd-induced lipid peroxidation

Although Cd is a non redox metal, increased lipid peroxidation as a result of Cd exposure has been observed in various in vitro and in vivo studies. Our investigations suggest the development of early oxidative stress in livers of mice after acute intoxication with Cd [18]. Recently, efforts were made to determine whether Mg can reduce these effects of Cd. The results of Boujelben et al. [47] showed that injections of Mg-sulfate lowered the Cd content in the kidney, liver and testis in a dose-dependent manner and the Cd-induced lipid peroxidation in liver and kidney. In testis, the protective effect of Mg was found only during the early phase of Cd-poisoning. They concluded that Mg supplementation can reduce Cd accumulation in organs and lipid peroxidation related to Cd administration. Our own study conducted on mice also showed that Mg supplementation reduced Cd accumulation in kidney [57]. Furthermore, under our experimental conditions, exposure to Cd induced time-dependent changes of GSH levels in the tissues of mice. Mg pretreatment reduced changes of GSH content in liver and kidney, observed in acute cadmium intoxication. Subacute Cd intoxication induced diminished renal GSH levels compared with the controls, whereas increased GSH levels were observed in liver and testes. Mg was efficient in restoring renal and testis GSH levels towards control levels, but did not affect hepatic GSH levels [77]. We concluded that excessive Mg intake reduces, at least partly, Cd induced changes in renal and testes GSH content.

Conclusions and perspectives

One of the greatest challenges in the field of Cd toxicology remains the identification and under-
standing of the molecular mechanisms by which Cd produces its adverse effects. Among them, interactions between Cd and essential metals, including Mg, could be of particular importance. As Mg deficiency is a possible consequence of Cd exposure, a higher intake of this bioelement is needed for people occupationally exposed or living in areas polluted by Cd. Moreover, Mg supplementation was demonstrated to have protective effects against Cd accumulation in the body and against its toxicity. Besides, Mg is a bioelement with a wide therapeutic window with few severe side effects. All these facts suggest that Mg could be utilized in the prevention and treatment of the adverse effects of exposure to Cd. Thus, the therapy of Cd intoxications, a very important issue in toxicological practice, could be, at least partly, dealt with. In this respect, it is crucial to initiate further research on the mechanisms of Cd induced toxicity and, especially, on the important antagonism between Cd and Mg, in order to develop a new approach to the therapy of Cd poisoning.

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