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TOXIC AND ESSENTIAL METAL INTERACTIONS

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ABSTRACT

Cadmium, lead, mercury, and aluminum are toxic metals that may interact metabolically with nutritionally essential metals. Iron deficiency increases absorption of cadmium, lead, and aluminum. Lead interacts with calcium in the nervous system to impair cognitive development. Cadmium and aluminum interact with calcium in the skeletal system to produce osteodystrophies. Lead replaces zinc on heme enzymes and cadmium replaces zinc on metallothionein. Selenium protects from mercury and methylmercury toxicity. Aluminum interacts with calcium in bone and kidneys, resulting in aluminum osteodystrophy. Calcium deficiency along with low dietary magnesium may contribute to aluminum-induced degenerative nervous disease.

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INTRODUCTION

Nutritionally essential metals may modify health risks from exposure to nonessential toxic metals. Although the basic role of nutritionally essential metals is to provide some component of a vital biochemical or enzymatic reaction, a number of metabolic interactions between nutritionally essential and nonessential toxic metals may reduce the health hazard of the toxic metal. This is not surprising in that some toxic metals and nutritionally essential metals share common chemical characteristics. This chapter identifies and defines the site of the interaction where evidence is available. Interactions between metabolically related essential metals per se—e.g. copper-zinc, iron-copper, etc—are beyond the scope of this chapter. Also, potential interactions between exclusively toxic metals are not considered, because for the most part such interactions, if they occur, are not well understood.

The toxic nonessential metals—aluminum, cadmium, mercury, and lead—are characterized as having no demonstrated biological requirement in humans, and exposure is associated with recognizable toxicity. Also, severity of toxicity increases with increases in dosage. Although there may be some lower limit of exposure at which toxicity may not be detected (threshold), there may be no level at the molecular level that does not have an adverse effect (37).

The best-defined and clinically important relationships between nutrition and toxic metals are shown in Table 1. These are the most-studied metal-nutrient interactions, and there is both experimental and clinical evidence that these nutritional factors have an impact on health outcomes from toxic metal exposures.

Table 1 Toxic-essential metal interactions[a]

Toxic metal	Essential metal	Health effect
Cadmium	Zinc	Nephrotoxicity
	Iron	
Lead	Calcium	Cognitive/behavioral
	Iron	effects in children
	Zinc	
Mercury	Selenium	CNS toxicity
Aluminum	Iron	CNS toxicity
	Calcium	Osteodystrophy
	Magnesium	
	Manganese	

[a]CNS, Central nervous system.

CADMIUM

Cadmium is a ubiquitous environmental pollutant (18, 71). It is nutritionally nonessential and toxic, and it interacts with the metabolism of three essential metals: calcium, zinc, and iron. Cadmium's pathway to man is from food, particularly leafy vegetables, grains, and cereals. The tobacco leaf is, in this sense, a leafy plant and contains substantial amounts of cadmium, so pack-a-day cigarette smokers virtually double their cadmium intake. Cadmium accumulates in the liver and kidneys and has a long biological half-life, from 17–30 years in man. Toxicity involves two organ systems, the renal and skeletal systems, and is largely the consequence of the interactions between cadmium and essential metals, particularly calcium.

Interactions with Calcium Metabolism

IN KIDNEYS Cadmium interferes with calcium and vitamin D metabolism in the kidney. Epidemiologic studies in Belgium of people living in communities where there has long been cadmium pollution from nonferrous metal refineries have found hypercalciuria, particularly in older women (12, 13). Whether the hypercalciuria is severe enough to enhance susceptibility to osteoporosis is currently being studied. This may be the "forme fruste" of a much more severe bone disease discovered in Japan, called Itai-Itai disease, which is thought to be due to excess cadmium exposure from rice and to nutritional deficiencies of calcium, vitamin D, zinc, and iron (71). Both the hypercalciuria in Belgium and Itai-Itai in Japan occur in older women who have borne children.

IN BONE Interactions between cadmium and calcium in bone may result in disorders of bone metabolism. Cadmium deposited in osteoid tissue interferes with calcification, decalcification, and bone remodeling (8). There is some debate as to whether the primary effect of cadmium on calcium metabolism is due more to its effect on kidneys or to its effect on bone. It has been hypothesized that renal loss of bone minerals produces osteopenia and, eventually, osteomalacia (71). However, experimental evidence summarized by Bhattacharyya et al (8) suggests that the calcium release from bone occurs prior to any evidence of a renal effect. In some studies, dietary cadmium inhibits the gastrointestinal absorption of calcium, probably through inhibition of 1,25-dihydroxyvitamin D (2). Hypocalcemia in response to cadmium exposure occurs after the onset of cadmium-induced release of bone mineral (8). Also, bone changes occur with no concomitant changes in concentrations of either 1,25-dihydroxyvitamin D or parathyroid hormone, two hormones expected to increase in response to a calcium deficiency caused by inadequate intestinal absorption. Although cadmium interferes with bone calcium metabolism and osteopenia is enhanced by cadmium nephropathy and calcium deficiency, the effect of cadmium on the gastrointestinal absorption of calcium is not clear.

Interactions with Zinc Metabolism

Interactions between zinc and cadmium metabolism are related to sharing of binding to metallothionein, a low-molecular-weight protein that binds zinc and copper and that may assist in the transport and storage of these essential metals (20, 59). Cadmium may also induce metallothionein and share binding on the protein with zinc. Cadmium bound to metallothionein in liver and kidney epithelial cells is thought to be nontoxic, but cadmium in plasma bound to metallothionein is toxic to the renal tubule while being excreted in urine (17).

Effects of Pregnancy

Pregnant rats exposed to cadmium have blood cadmium-metallothionein levels higher than those that occur in rats not exposed to cadmium, which suggests that during pregnancy cadmium absorption from the gastrointestinal tract is increased along with zinc and copper (17). Pregnancy increases cadmium accumulation in kidneys (7) and mobilizes copper and zinc bound to metallothionein (17). This might be expected in that metallothionein has a role in storage of the essential metals zinc and copper and in their transport from the placenta to the fetus, where they are required for growth and development. The source of the increase in metallothionein in a mother's plasma is not known, but some may come from the placenta, where it is synthesized by trophoblasts. The interactions between cadmium and zinc and copper in the placenta are not understood, but cadmium bound to metallothionein in the placenta does not cross the placenta. The newborn is virtually cadmium-free, whereas zinc and copper are readily supplied to the fetus (39).

Effects of Iron Deficiency

Iron deficiency increases cadmium absorption from the gastrointestinal tract. It has been shown both in experiment animals and in humans that cadmium absorption from the intestinal tract is inversely related to blood ferritin levels (28). The mechanism for this relationship is not known.

LEAD

Lead toxicity affects several organ systems, including the nervous, hematopoietic, renal, endocrine, and skeletal, depending on the age of the subject and the size of the dose, but the effect of major concern today is the impairment of cognitive and behavioral development in infants and young children in the general population (51). Effects occur from low-level exposures from various environmental sources, including lead-based paint and household dust in homes containing surfaces covered with lead-based paint. Lead in air, food, and water is also of concern, but hazards from these sources as well as lead in dust have

been greatly reduced by the removal of lead from gasoline. The elimination of lead solder from food cans has reduced the hazard of exposure to lead from canned food, in particular canned milk for infant formula. There is increasing awareness of the hazard from lead in tap water contaminated from solder and lead-containing fittings in residential plumbing. Lead in water is more efficiently absorbed than lead in food is; lead in water used for infant formula is an additional hazard.

Measurable effects occur with blood lead levels in the 10- to 15-μg/dl range, and more than a million children in the United States have blood levels in this range or higher (1, 51). Nutritional deficiencies of essential metals can increase the hazard from lead exposure by enhancing absorption and toxicity of dietary lead. The essential metals with the most marked influence on blood lead levels and toxic effects are dietary levels of calcium, iron, and zinc.

Interactions with Calcium

Lead and calcium interactions are probably the most studied nutritional factors affecting lead toxicity, both clinically and experimentally. There are several suggestions in the lead toxicity literature that the two metals are metabolically related. Aub and colleagues, in 1926 (3), pointed out that physiologically, the "Pb stream" follows the "calcium stream," and in 1970, Six & Goyer (64) showed that a low-calcium diet containing varying levels of lead fed to rats resulted in considerably higher blood and tissue levels of lead than those that occurred in rats fed a normal calcium diet. This study also showed that the increase in lead content of the kidneys was considerably greater than the increase in bone lead. The importance of this is that the toxic effects of lead are related to blood lead levels and, in turn, soft tissue levels, and that low dietary calcium increases lead in critical organs. There are reports of many other experimental studies showing that absorption of lead by the gastrointestinal tract is inversely related to calcium content of the diet (6, 48). Bogden et al (10) have shown an inverse relationship between brain lead and dietary calcium, confirming that nutritional deficiency of calcium not only elevates blood lead levels, it also increases lead in the critical organ for toxicity in infants and young children.

Although it is not possible to mimic the animal studies in people, balance studies conducted by Ziegler et al (74) showed an inverse relationship between dietary calcium and lead absorption and retention. It has also been shown that milk alone may not be an effective source of calcium for this purpose, because other dietary constituents of milk such as lactose and fat may actually enhance lead absorption (63). Mahaffey et al (47) reviewed the relationship between blood lead levels and dietary calcium intake in about 3000 children examined as part of the second National Health and Nutrition Examination Survey (NHANES II). A significant and independent inverse association was observed

between dietary calcium intake, estimated from dietary recall data, and blood lead level in this large, stratified, national probability sample. The importance of adequate dietary calcium in the prevention of childhood lead toxicity is now well accepted, and children at risk are provided calcium supplements in state and city lead prevention programs. The Centers for Disease Control guidelines for prevention of childhood lead poisoning recommends adequate dietary calcium and iron as measures to prevent lead toxicity (15).

Although there is considerable support for the importance of adequate dietary calcium, there is little information regarding the effect of excess calcium, either on lead absorption or on changing tissue levels of lead. Barton (5) reported that increasing the calcium dose in the intubation media reduced lead uptake from isolated intestinal loops. Bogden et al (10) found a small but significant reduction in blood lead in rats receiving a moderately heavy dietary calcium (2.5%) compared to blood lead levels in rats receiving 0.5% dietary calcium. In studies of adults, Blake & Mann (9) found that ingestion of milk does reduce the short-term retention of ingested lead. These studies suggest that excess calcium may lower lead absorption and blood lead levels, but the influence of excess calcium on reducing the effects of lead toxicity seems considerably less dramatic than the effect of enhancing toxicity by less-than-adequate dietary calcium.

Calcium-lead interactions are also related to critical clinical effects of lead at the cellular and molecular level, particularly for effects of lead on neurodevelopment and neuro-function, as summarized by Goyer (38) and Verity (67) (Table 2). Lead interferes with neurotransmitter kinetics, including dopamine and γ-aminobutyric acid (50), and blocks entry of calcium into nerve terminals (62) and impairs normal calcium homeostasis in cells, which is essential for normal cell function, by competing with calcium for uptake by calcium channels (61). Lead also inhibits all calcium channel subtypes equally (4). It has been found that calcium channel–modifying drugs have similar effects on lead entry into cells (62).

Lead blocks calcium efflux from cells probably by substituting for calcium in calcium-sodium ATP pumps (62). This is probably one of the mechanisms

Table 2 Lead effects on cellular calcium metabolism[a]

Interferes with neurotransmitter kinetics
Blocks voltage-dependent calcium membrane channels
Substitues for calcium in calcium-sodium ATP pump
Competes for Ca-binding protein sites
Competes for uptake by mitochondria
Binds to second messenger calcium receptors
e.g. calmodulin, protein kinase C

[a]Modified from Goyer (38) and Verity (67).

by which lead interacts with calcium in the intestine; the less calcium there is in the diet, the more lead is absorbed (5). The other mechanism at the gut level is lead competing with calcium for binding sites on calcium-binding proteins (30).

It was found many years ago that mitochondrial respiration and oxidative phosphorylation were decreased in renal tubular cells isolated from lead toxic rats (36). Subsequent studies have shown that lead inhibits calcium uptake in brain mitochondria (34) and may even displace calcium within the mitochondrion (42).

Probably the most critical interaction between lead and calcium occurs within cells where lead interferes with calcium receptors that are coupled with second-messenger functions. Lead-related interference with calcium homeostasis and calcium messenger systems has been reviewed in detail by Pounds et al (56), and by Bressler & Goldstein (11). Intracellular calcium signals are received by a variety of calcium receptor proteins. The two that have received the most attention in relation to lead effect are calmodulin and protein kinase C. Calmodulin serves as a sensor for the concentration of calcium inside the nerve terminus, stimulating neurotransmitter release. Lead acts by displacing calcium ions bound to calmodulin (40). Protein kinase C is activated by calcium, and lead appears to be more active than calcium in increasing the activity of this enzyme. Protein kinase C–mediated responses include cell division and proliferation, cell-cell communications, and organization of the cytoskeleton. Protein kinase C activates kinases in the nerve terminus that phosphorylate specific brain proteins in synaptic vesicles, resulting in the increased release of neurotransmitters (35). Regulation of neurotransmitter release is important in the modulation of cognitive and behavioral function. It has been suggested that increased vascular reactivity in lead-induced hypertension is due to increased protein kinase C and to lead-induced changes in cellular calcium metabolism (16).

Interactions with Iron

Iron deficiency has been shown in experiment animals to increase lead absorption from the intestinal tract (65), but attempts to demonstrate this relationship in human populations have not been consistent (46). Participation of children who are at risk to excess lead exposure in the Special Supplemental Food Program for Women, Infants and Children (WIC Program), precludes the demonstration of the impact of iron deficiency on increased lead absorption (25). The mechanism by which lead affects iron absorption is uncertain. A possible connection between intestinal ferritin and iron has been suggested for some time (27). Kochen & Greener (45) have shown that lead competes with iron for ferritin binding sites. Whether transferrin in the intestinal mucosa is also involved in

some way has not been demonstrated. Diaz-Barriga et al (23) found a negative correlation between blood lead levels and the ratio of iron-to-iron-binding capacity for children between ages 9 and 11 years of age.

Because iron deficiency is a common nutritional problem among the same children at risk for lead toxicity, it is now a general practice to supplement the diets of these children with iron as well as calcium. The relationship between iron deficiency and the impaired cognitive and behavioral development seen in children with excess lead exposure is complex in that iron deficiency in itself may impair early mental development (72).

Interactions with Zinc

Lead and zinc interactions are not as well defined as those between lead and calcium and lead and iron. It has been shown experimentally that lead increases zinc excretion (68), and that zinc deficiency enhances lead absorption (38). Prasad et al (57) found that zinc deficiency decreases the activity of thymulin, a zinc-containing nonapeptide derived from the epithelium of the thymus gland, and Hemalatha et al (41) suggest that mild zinc deficiency in children may be recognized by correlating plasma and leukocyte zinc levels with serum thymulin levels.

There is a close inverse relationship between blood lead and activity of zinc-containing heme enzymes, particularly δ-aminolevulinic acid, which suggests that lead replaces zinc in these enzymes. Oral administration of zinc sulfate following chelation therapy has been found to significantly increase δ-aminolevulinicacid dehydratase activity (26).

Interactions with Copper in Human Milk

The content of lead and copper in human milk is inversely related. An important observation regarding lead-copper interactions concerns lead and copper in human milk. Human milk contains relatively low levels of both iron and copper, whereas both minerals are very important to the developing infant. Kies & Umoren (43) found that as the lead content of human milk increased, the amount of copper in the milk decreased. Whether lead-copper interaction is at the site of absorption of copper from the gastrointestinal tract or at some other metabolic or transport site has not been determined. Lead-exposed rats have a significant decrease in hepatic copper (24). Rodents with lead toxicity have reduced plasma copper and ceruloplasmin levels (54), and the addition of dietary lead to copper-deficient animals reduces growth rate (55).

Interactions of Copper with Iron in Lead-Induced Anemia

There are a number of incompletely understood relationships between copper and iron and lead-induced anemia. Hematopoiesis is depressed in animals with low dietary copper and is further depressed by lead exposure, resulting

in anemia (44). Lead inhibits ferrochelatase activity. Ferrochelatase is an iron-containing enzyme and is needed to incorporate iron into the hemoglobin molecule. Lead replaces iron in the ferrochelatase molecule. The activity of the enzyme is restored by adding iron in vitro, but this does not occur in vivo and without the coadministration of copper. Inhibition of ferrochelatase by lead may be overcome in rats by feeding them copper (66).

MERCURY

Interactions with Selenium

Several nutrients have been found to affect the toxicity of mercury. Of these, selenium has been the most widely studied. Parizek & Ostadalova (52) were the first to show that selenium protected against acute toxicity of mercury. The mechanism for this effect is unknown, but it has been noted that vitamin E and other antioxidants also decrease mercury toxicity (21, 69). This prompts the hypothesis that selenium may decrease mercury toxicity by counteracting the effects of free radicals generated by mercury toxicity to cell membranes (32). Mercury alters the cellular oxidant state by decreasing activity of enzymes of glutathione (GSH) biosynthesis. Mercuric chloride administered to rats causes a marked decrease in activities of glutathione reductase and δ-glutamylcysteine synthetase (49) in kidneys. However, when rats were given selenium after mercury (2:1 ratio of mercury to selenium), the depression in activities of GSH synthesis enzymes was blocked. Chmielnicka (19) found that sodium selenite given jointly with mercuric chloride decreased the rise in urinary excretion of endogenous copper and zinc induced by renal mercury toxicity. It is suggested that sodium selenite diminishes the affinity of inorganic mercury for the kidneys and reduces the level of mercury bound to renal metallothionein. In general, selenium has a protective effect in that it delays the onset of mercury toxicity or reduces the severity of the effects of both inorganic forms of mercury and methylmercury. It has been suggested that high selenium levels in fish may be protective against toxicity of the methylmercury (33). The influence of selenium in tuna and other seafood on risk of health effects from dietary consumption has not been determined.

There is also evidence that various forms of selenium, including selenate and selenide, when administered to rats together with mercuric chloride, reduce the toxicity of both selenium and mercury, probably by forming a mercury-selenium complex that can be detected in nuclei of renal tubular cells by electron microscopy (14). The presence of both elements in the nuclear inclusion bodies has been detected by X-ray microanalysis. The metals are probably complexed in a protein matrix that has not been identified but may be similar to lead or bismuth inclusion bodies (29, 36).

ALUMINUM

Aluminum is a toxic metal, but it generally does not cause adverse health effects among people in the general population. On the other hand, as the constituent of common sand (aluminum silicate), it is one of the most abundant metals in the earth's crust, and inhaled and ingested aluminum compounds are absorbed in the body to some extent. Elimination of aluminum from the body is mainly via urine. There is some evidence for a metabolic relationship between aluminum and iron, calcium, magnesium, and manganese (31).

Interactions with Calcium, Magnesium, and Manganese

A unique environmental combination of low dietary intake of calcium and magnesium, together with high concentrations of aluminum and manganese in drinking water, has been proposed as a factor in the incidence of amyotrophic lateral sclerosis and Parkinsonian-dementia in specific areas of the western Pacific (53). Experiments with primates and rabbits fed diets deficient in calcium and magnesium together with aluminum and manganese have shown increased aluminum accumulation in some organs, particularly in the kidneys and in bone, but they failed to produce central nervous system changes (70). However, a recent study by Yasui et al (73) in rats led to high concentrations of manganese and aluminum in the frontal cortex. The authors concluded that these metal-metal interactions may lead to unequal distributions of aluminum and manganese in bones and the central nervous system, resulting in neural degeneration. Aluminum has been linked to the pathogenesis of Alzheimer's disease, but this relationship is controversial (22) and does not appear to be related to any interaction with essential trace minerals. Humans with impaired kidney function and in renal failure (uremia) or on hemodialysis may accumulate aluminum to levels toxic to bone metabolism, resulting in a form of osteodystrophy (8), and in the central nervous system, producing impaired memory, dementia, aphasia, ataxia, convulsions, and characteristic electroencephalogram changes (22). Aluminum also slows calcification of new bone and becomes deposited in the bone matrix in place of calcium. However, there does not appear to be any direct interaction between calcium and aluminum, and the effect of aluminum on bone is now thought to be the result of cellular toxicity (60).

Interactions with Iron

Aluminum behaves similarly to iron in many biological systems, and iron deficiency increases the absorption of iron in rats. In this way aluminum may indirectly affect the toxicity of aluminum. It has been suggested that aluminum is taken up in the gut by specialized iron-absorption pathways. Although iron uptake by the intestine is a regulated process dependent on the needs of the body, there is no evidence that absorption of aluminum is regulated. The major

plasma binder of aluminum is transferrin, an iron-transport protein that also binds with other metals, including aluminum, at two specific binding sites (22). Iron-to-aluminum ratios in different organs vary widely. High ratios occur in the spleen, liver, and kidneys and seem to be related to the high iron concentrations in these organs. High ratios in heart and brain muscle are due to low aluminum concentrations in these tissues, whereas low ratios in the intestine, lungs, skin, and hair are associated with relatively high aluminum concentrations in these organs. Aluminum also increases in the liver, along with iron in hemochromatosis and other disorders of iron overload. Roskams & Conner (58) have suggested that aluminum's toxicity in the brain may be due at least in part to disruption of normal iron homeostasis and iron-dependent cellular metabolism.

SUMMARY

Cadmium toxicity affects calcium metabolism either by direct toxicity to bone or indirectly from renal toxicity. Zinc and cadmium metabolism are related via metallothionein; both induce synthesis of metallothionein. Calcium, iron, and zinc deficiency enhance cadmium and lead toxicity by increasing absorption of the toxic metals and by exchanging with the essential cation on biochemically active sites, including receptor proteins in the brain. Selenium protects from mercury and methylmercury toxicity, probably by preventing damage from free radicals by increasing the mercury-induced depression in glutathione-synthesizing enzymes and by forming inactive selenium-mercury complexes. There is some evidence for a metabolic relationship between aluminum, iron, calcium, magnesium, and manganese in bone and the central nervous system. The influence of these relationships on aluminum toxicity is uncertain.

From what is known about toxic-essential metal interactions, it is now clear that essential metal deficiencies do influence health effects from toxic metal exposures and that adequate dietary essential metals are necessary for prevention and intervention of metal toxicities.

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