Nutrition and metal toxicity\textsuperscript{1,2}

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ABSTRACT  Lead, cadmium, and mercury are toxic metals that are not essential for nutrition. However, the toxic effects of these metals may be mediated or enhanced by interactions or deficiencies of nutritionally essential metals. Lead competes with calcium, inhibiting the release of neurotransmitters, and interferes with the regulation of cell metabolism by binding to second-messenger calcium receptors, blocking calcium transport by calcium channels and calcium-sodium ATP pumps, and by competing for calcium-binding protein sites and uptake by mitochondria. Dietary deficiencies of calcium, iron, and zinc enhance the effects of lead on cognitive and behavioral development. Iron deficiency increases the gastrointestinal absorption of cadmium, and cadmium competes with zinc for binding sites on metallothionein, which is important in the storage and transport of zinc during development. Selenium protects from mercury and methyl mercury toxicity by preventing damage from free radicals or by forming inactive selenium mercury complexes.  

KEY WORDS  Nutrition, deficiencies, toxicity, lead, cadmium, mercury, calcium, iron, zinc, selenium

Introduction

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. The three toxic metals lead, cadmium, and mercury have no nutritional requirement and there may be no tissue concentration at which there is no toxic effect, only minimum concentrations at which toxic effects are observed with available methods of detection. Also, severity of toxic effects increases with dose (1). Interactions or deficiencies of essential metals may have a role in mediating or enhancing the severity of the toxic effect.

Environmental lead exposure and toxicity

Lead toxicity affects several organ systems including the nervous, hematopoietic, renal, endocrine, and skeletal systems depending on the age of the subject and the lead dose, but the effect of major concern today is the impairment of cognitive and behavioral development in infants and young children (2). 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 are 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 is lead in food; lead in water used for infant formula is an additional hazard.

Measurable effects occur with blood lead concentrations in the 0.48–0.72 μmol/L (10–15 μg/dL) range and more than one million children in the United States have blood concentrations in this range or higher (2, 3). 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 concentrations and the most marked toxic effects are calcium, iron, and zinc.

Lead-calcium interactions

Lead-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. In 1926 Aub et al (4), pointed out that physiologically, the “Pb stream” follows the “calcium stream.” Some 25 y ago Six and Goyer (5) showed that a low-calcium diet containing varying amounts of lead fed to rats resulted in considerably higher blood and tissue concentrations of lead than occurred in rats fed a normal-calcium diet of 0.7%. Rats fed the low-calcium diet, which contained only 12 ppm lead, had blood and tissue concentrations of lead similar to those in rats receiving 200 ppm lead on a normal-calcium diet. This study also showed that the increase in the 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 concentrations and, in turn, to soft tissue concentrations and that low dietary calcium increases the con-
TABLE 1

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<tr>
<th>Toxic metal: essential metal</th>
<th>Health effect</th>
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<tr>
<td>Lead: calcium, iron, zinc</td>
<td>Cognitive and behavior effects in children</td>
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<tr>
<td>Cadmium: zinc, iron</td>
<td>Nephrotoxicity</td>
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<tr>
<td>Mercury: selenium</td>
<td>Central nervous system toxicity</td>
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centrations of lead in critical organs. Many other experimental studies have shown that absorption of lead by the gastrointestinal tract is inversely related to calcium content of the diet (6–8). More recently, Bogden et al (9) showed an inverse relationship between brain lead and dietary calcium, confirming that nutritional deficiency of calcium not only elevates blood lead concentrations but 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, Ziegler et al (10) conducted multiple (three to eight), 72-h metabolic balance studies on each of nine infants. Lead and calcium intakes from milk and other food items were measured and lead retention calculated as the difference between intake and excretion. The results of the study 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 (11). Mahaffey et al (12) reviewed the relationship between blood lead concentrations and dietary calcium intake in ~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 concentrations 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 the prevention of childhood lead poisoning recommend adequate dietary calcium and iron as measures to prevent lead toxicity (13).

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 changes in tissue concentrations of lead. Barton et al (8) reported that increasing the calcium dose in the intubation media reduced lead uptake from isolated intestinal loops. Bogden et al (9) found a small but significant reduction in blood lead in rats receiving a moderately high amount of dietary calcium (2.5%) compared with blood lead concentrations in rats receiving 0.5% dietary calcium. In studies of adults, Blake and Mann (14) found that ingestion of milk does reduce the short-term retention of ingested lead. These studies do suggest that excess calcium may lower lead absorption and blood lead concentrations but the influence of excess calcium on lead toxicity seems considerably less dramatic than the effect of less than adequate dietary calcium.

Calcium–lead interactions are also related to critical clinical effects of lead at the cellular and molecular level, particularly the effects of lead on neurodevelopment and neurofunction as summarized in Table 2.

Several years ago, Kostial and Vouk (15) showed that lead inhibits acetyl choline release from an in vitro preparation of cat superior ganglion and that this effect is reversed by increasing the calcium concentration in the media. Studies by others have shown that lead blocks entry of calcium into nerve terminals (16). Lead impairs normal calcium homeostasis in cells, which is essential for normal cell function by competing with calcium for uptake by calcium channels (17). Recent studies suggest that lead inhibits all calcium channel subtypes equally (18). Also, it has been found that calcium channel modifying drugs have similar effects on lead entry into cells (16).

Lead most likely blocks calcium efflux from cells by substituting for calcium in calcium-sodium ATP pumps (19). This is probably one of the mechanisms by which lead interacts with calcium in the intestine; the less calcium in the diet the more lead that is absorbed (25). The other mechanism at the gut level is lead competing with calcium for binding sites on calcium-binding proteins (20).

It was found many years ago that mitochondrial respiration and oxidative phosphorylation were decreased in renal tubular cells isolated from rats suffering from lead toxicity (21). Subsequent studies have shown that lead inhibits calcium uptake in heart mitochondria (22) and brain mitochondria (26) and may even displace calcium within the mitochondrion (27).

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 (28) and Bressler and Goldstein (29).

Intracellular calcium signals are received by a variety of calcium receptor proteins. The two that have received the most attention in relation to their effects on lead are calmodulin and protein kinase C. Calmodulin serves as a sensor for the free concentration of calcium inside the nerve terminal and stimulates neurotransmitter release. Lead acts by displacing calcium ions bound to calmodulin (23). Protein kinase C is activated by calcium, and lead appears to be more active than is calcium in increasing the activity of this enzyme. Responses mediated by protein kinase C include cell division and proliferation, cell-cell communications, and organization of the cytoskeleton. Protein kinase C activates kinases in the nerve terminal that phosphorylate specific brain proteins in synaptic vesicles, resulting in the increased release of neurotransmitters (24). 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

<table>
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<th>TABLE 2</th>
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<td>Interactions of lead with calcium metabolism</td>
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<td>1) Inhibits neurotransmitter release (15)</td>
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<td>2) Blocks calcium transport by calcium channels (16–18)</td>
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<td>3) Substitutes for calcium in calcium-sodium ATP pump (19)</td>
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<td>4) Competes for calcium-binding protein sites (20)</td>
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<td>5) Competes for uptake by mitochondria (20–22)</td>
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<td>6) Binds to second messenger calcium receptors, eg, calmodulin, protein kinase C (23, 24)</td>
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is due to increased protein kinase C and lead-induced changes in cellular calcium metabolism (30).

Iron deficiency and lead toxicity

Iron deficiency has been shown in experimental animals to increase lead absorption from the intestinal tract (31), but attempts to demonstrate this relationship in humans have not been consistent (32). Participation of children who are at risk of excess lead exposure in the Special Supplemental Food Program for Women, Infants and Children (WIC) precludes the demonstration of the impact of iron deficiency on increased lead absorption (33). The mechanism by which lead absorption is uncertain. A possible connection between intestinal ferritin and iron has been suggested for some time (34). Kochen and Greener (35) 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.

Given the knowledge that iron deficiency is a common nutritional problem in the same children who are at risk for lead toxicity, it is now a general practice to supplement 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 (36).

Lead and zinc interactions

Lead and zinc interactions are not as well defined as those between lead and calcium, and between lead and iron. It has been shown experimentally that lead increases zinc excretion (37) and that zinc deficiency enhances lead absorption (38). In a single-blind, case-control study, Lauwerys et al (39) were unable to demonstrate an effect of zinc supplementation on blood lead concentrations of adequately nourished workmen with moderate lead exposure. Whether lead supplementation influences blood lead concentrations in persons with zinc deficiency has not been determined. A constraint on the conduct of such a study is the difficulty in recognizing mild zinc deficiency. However, Prasad et al (40) have found that zinc deficiency decreases the activity of thymulin, a zinc-containing nonapeptide derived from the epithelium of the thymus gland; Hemalatha et al (41) suggest that mild zinc deficiency in children may be recognized by correlating plasma and leukocyte zinc concentrations with serum thymulin concentrations.

There is a close inverse relationship between blood lead and the activity of zinc-containing heme enzymes, particularly δ-aminolevulinic acid, suggesting that lead replaces zinc in these enzymes. Oral administration of zinc sulfate after chelation therapy has been found to significantly increase δ-aminolevulinic acid dehydratase activity (42).

Cadmium and essential metal interactions

Cadmium is a ubiquitous environmental pollutant (43). It is a nonessential and toxic metal and interacts with the metabolism of three essential metals—calcium, zinc, and iron. Pathways to humans are 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 that cadmium uptake is virtually doubled in a pack-a-day smoker. Cadmium accumulates in liver and kidney and has a long biological half-life from 17 to 30 y in man. Toxicity involves two organ systems, kidneys and bone. In the kidney it produces proximal tubular dysfunction so that there is a decrease in resorption of amino acids, glucose, phosphate, and low-molecular-weight proteins. Epidemiological studies in Belgium of people living in communities where there is historical cadmium pollution from nonferrous metal refineries have found hypercalciuria particularly in older women (44). Whether the hypercalciuria is severe enough to enhance susceptibility to osteoporosis is now 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 cadmium in rice and nutritional deficiencies of calcium, vitamin D, zinc, and iron (43). Both hypercalciuria in Belgium and Itai-Itai in Japan occur in older women who have borne children.

Cadmium has an inhibitory effect on intestinal calcium transport stimulated by vitamin D in rats (45). There is also an interaction between cadmium and calcium in bone. Cadmium deposited in osteoid tissue may interfere with calcification, decalcification, and bone remodeling (46). Zinc and cadmium metabolism are related to the metallothioneins, a group of low-molecular-weight proteins that bind zinc and copper and that may assist in the transport and storage of these essential metals (47, 48). 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 (49). An interesting recent discovery is that pregnancy mobilizes copper and zinc bound to metallothionein (50). This might be expected in that metallothionein has a role in storage of the essential metals zinc and copper in placenta to the fetus, where they are required for growth and development. The source of the increase in metallothionein in mother’s plasma is not known but some may come from the placenta, where it is synthesized by trophoblast. 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 (51). Pregnant rats exposed to cadmium have blood cadmium-metallothionein concentrations that are higher than those that occur in rats not exposed to cadmium, suggesting that during pregnancy cadmium absorption from the gastrointestinal tract is increased along with zinc and copper (50, 52).

Iron deficiency increases cadmium absorption from the gastrointestinal tract. It has been shown in both experimental animals and humans that cadmium absorption from the intestinal tract is inversely related to blood ferritin concentrations (53). The mechanism for this relationship is not known.

Mercury-selenium interactions

Several nutrients have been found to affect the toxicity of mercury. Of these, selenium is the most widely studied. Parizek
and Ostadalova (54) 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 (55), prompting the hypothesis that selenium may decrease mercury toxicity by counteracting the effects of free radicals generated by mercury toxicity to cell membranes (56). 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 methyl mercury. It has been suggested that high selenium concentrations in fish may be protective against toxicity of methyl mercury (57). The influence of selenium in tuna and other seafood on the 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 the nuclei of renal tubular cells by electron microscopy (58). The presence of both elements in the nuclear inclusion bodies has been detected by x-ray micro-analysis. The metals are probably complexed in a protein matrix that has not been identified, perhaps one that is similar to lead or bismuth inclusion bodies (21, 59).

Summary

Calcium, iron, and zinc deficiency enhance lead toxicity by increasing lead absorption and by trading places with the essential cation on biochemically active sites including receptor proteins in the brain.

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. However, whereas cadmium metallothionein complexes may be protective of cell toxicity within cells, the cadmium-metallothionein complex is very toxic to renal tubular cells when excreted in glomerular filtrate.

Iron deficiency increases gastrointestinal absorption of cadmium. Selenium most likely protects from mercury and methyl mercury toxicity by preventing damage from free radicals or by forming inactive mercury selenium complexes.

It is now clear, from what is known about toxic-essential metal interactions, that essential metal deficiencies do influence risk assessments for toxic metal exposures. The corollary to this is that it is extremely important to maintain optimal nutritional status for essential metals to minimize risk from toxic metal exposure.

References