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Metabolic Interactions between Metals and Metalloids

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The experimental evidence obtained with laboratory animals which shows that the toxicities of lead, cadmium, and mercury can be increased by deficiencies of certain essential nutrients such as calcium, iron, zinc, and selenium is briefly reviewed. An idealized theoretical model which indicates the possible influence of multiple nutritional deficiencies on the toxicity of a heavy metal is presented. It is suggested that multiple marginal nutritional deficiencies may be of importance in determining the response of humans to the toxic effects of various heavy metal pollutants.

Toxicologists, like most scientists, have taken a reductionistic approach with laboratory animal models, examining singly the biological effects of this or that toxic substance. In the past, this approach has been useful and even necessary to identify specific effects, but human beings are often exposed to various combinations of environmental toxicants. Also, the ability of humans to resist toxic metals may be influenced by their nutritional status. The consumption of highly refined foods is increasing and more marginal trace element deficiencies are being discovered in man. This is especially true for the industrialized countries in which diets high in fat and refined carbohydrate are consumed.

This paper first reviews briefly the laboratory evidence that heavy metal toxicity can be increased by deficiencies of essential minerals. A simple theoretical model of nutrient–heavy metal interactions follows. A final section speculates on possible nutrient–heavy metal interactions in man.

Laboratory Animal Models

Lead

Lead toxicity is increased by deficiencies of essential minerals including calcium, iron, or zinc. For example, only 12 ppm lead in the drinking water caused renal intranuclear inclusion bodies in calcium-deficient rats, whereas 200 ppm lead were needed to induce inclusions in rats with a normal calcium intake (*1*). Quarterman and Morrison (*2*) suggested that calcium deficiency increased lead toxicity by stimulating the synthesis of intestinal calcium binding protein thereby increasing lead absorption. Iron deficiency may also increase the toxicity of lead by increasing its absorption, but iron deficiency greatly increased lead deposition only in the bones while calcium deficiency increased lead deposition markedly in both the bones and kidneys (*1*). Cerklewski and Forbes (*3*) found that the severity of lead toxicity in rats decreased as the level of dietary zinc increased, possibly due to an inhibition of the intestinal absorption of lead. However, zinc, when added either *in vitro* (*4*) or *in vivo* (*5*), can prevent the inhibition of δ-aminolevulinic acid dehydratase by lead; apparently zinc may have more than one antagonistic action against lead.

Cadmium

Cadmium toxicity also is increased by dietary deficiencies of essential minerals, such as iron, zinc, copper, or calcium (*6*). Iron deficiency may potentiate the toxicity of cadmium by stimulating its gastrointestinal absorption (*7*). On the other hand, both injected and oral iron protect against cadmium so the heavy metal may also affect iron utilization by the tissues (*8*). Calcium deficiency increased cadmium deposition in the tissues (*9*) but did not influence the effects of cadmium on the renal vasculature (*10*).

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Selenium

Selenium protects against the toxicity of several metals including mercury and cadmium. The antagonism between selenium and mercury was first demonstrated at high dose levels (*11*). Parizek also postulated that dietary selenium might protect organisms against heavy metal environmental pollutants. Ganther et al. (*12*) showed that nutritional levels of selenium protected against the chronic toxicity of the environmentally relevant methylmercury. The mechanism by which selenium decreases mercury toxicity is not known, but the earlier suggestion that selenium diverted mercury from sensitive cellular proteins is not valid for low doses (*13*). Vitamin E also protects against methylmercury (*14*). This may provide an important clue to the mechanism of the protective effect of selenium. Both selenium and vitamin E decrease the toxicity of methylmercury to nervous tissue grown in culture (*15*).

Parizek and co-workers (*11*) pioneered much of the early work on the antagonism between selenium and cadmium at high dose levels. Later work showed that lower levels of selenium reduced the hypertension in rats caused by chronic administration of cadmium in the drinking water (*16*). As in the case of mercury, the metabolic antagonisms between high doses of selenium and cadmium are not observed at lower dose levels, so the mechanism whereby selenium and cadmium interact at low levels is still unknown (*13*).

Although selenium protects against mercury and cadmium poisoning, it has little or no protective effect against lead toxicity (*17*). On the other hand, vitamin E deficiency increases the response of rats to lead poisoning (*18, 19*).

The toxicity of selenium is strongly antagonized by arsenic but arsenic has no influence on the induction of selenium deficiency (*20*). Arsenic may protect against selenium toxicity by promoting its biliary excretion (*21*).

Theoretical Model

Figures 1 and 2 are idealized representations of the influence of nutritional status on the exposure-response curve of heavy metal toxicants. Figure 1 consists of a family of exposure-response curves which depict three degrees of response (Y_1, Y_2, and Y_3) at a given exposure to a certain toxic metal (X_1) depending on the slope of the particular curve. The slopes of the curves are determined by the nutritional status of the animal. Curve *A* represents the exposure-response curve of animals fed a nutritionally adequate diet. For a given exposure (X_1) the response (Y_1) is observed. Curve *B* depicts the exposure-response curve of animals fed a diet low in some nutrient a deficiency of which increases the toxicity of the heavy metal. In this case equivalent exposure (X_1) yields a greater response (Y_2). Curve *C* is the exposure–response curve of animals lacking two nutrients both of which influence the tox-

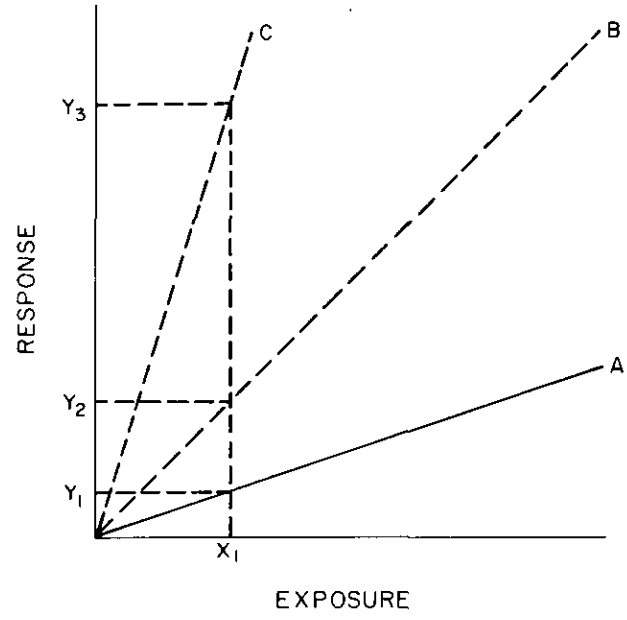

FIGURE 1. Nutrient–heavy metal interactions: variable response at constant exposure.

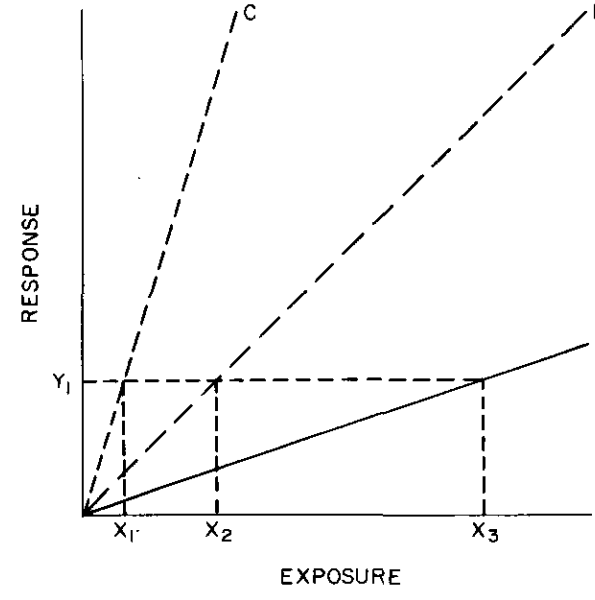

FIGURE 2. Nutrient–heavy metal interactions: constant response at variable exposure.

icity of the heavy metal. Now the same exposure (X_1) causes a marked response (Y_3). In other words, the biological response to a given exposure of heavy metal is intensified as a result of multiple nutritional deficiencies in the test animal. The work of Welsh and Soares (*14*) shows that such a theoretical situation actually exists. Their data show that the response of quail to methylmercury (mortality) was increased by feeding a diet low in selenium and could be increased further by feeding a diet low in both selenium and vitamin E. In our own laboratory we have shown that the response of vitamin E-deficient rats to lead poisoning (*18*) can be amplified by concurrent calcium deficiency (Levander et al., unpublished observations). These experiments suggest that the effects of nutritional deficiencies on toxic response might be additive thereby rendering an organism suffering from multiple deficiencies highly vulnerable to the toxic effects of a heavy metal.

Figure 2 presents another perspective on nutrient/toxicant interactions and depicts constant response at variable exposure. The concept is that the extent of exposure needed to elicit a given response can be decreased by changing the nutritional status of an animal. For example, Mahaffey (*1*) showed that the amount of lead needed to induce renal inclusion bodies is markedly reduced in calcium-deficient rats (shift from curve *A* to curve *B* in Fig. 2). An interesting experiment would be to test the effect of a combined iron and calcium deficiency on this response (possible shift from curve *B* to curve *C*).

Although Figures 1 and 2 were designed primarily to illustrate the effect of nutritional status on toxic response, they also could be used to illustrate synergistic toxic responses. If a biological response common to lead, cadmium, and mercury could be defined, then curve *A* could represent the response to one metal, curve *B* to two metals, and curve *C* to three metals. Few have studied possible synergistic effects of these metals, but Ferm (*22*) demonstrated a synteratogenic effect between lead and cadmium. Also, Murthy et al. (*23*) showed that lead and cadmium had additive effects on copper metabolism. Synergistic effects between various toxicants may not always be readily predictable, however, as evidenced by the recent discovery of an interaction between lead and benzene (*24*).

Of course, the above theoretical representations are based on simplifying assumptions, such as linearity of the exposure–response curve, absence of threshold effects, etc. Those assumptions, however, do not invalidate the model. But the model might be criticized because all individual nutritional deficiencies, which by themselves increase heavy metal toxicity, may not necessarily have additive effects in combination.

Possible Human Health Significance

The above discussion suggests that multiple marginal nutritional deficiencies might have deleterious effects in humans exposed to heavy metal contaminants. The possible significance of this problem to public health is clear because borderline deficiencies of calcium, iron, and zinc, all of which increase the toxicities of lead and cadmium, have been reported in the industrialized (and hence the most heavily polluted) countries. Moreover, the nutritional need for selenium and vitamin E, both of which protect against methylmercury poisoning, may be influenced by exposure to atmospheric oxidants such as ozone or nitrogen oxides. Also, vitamin E affects lead toxicity (*18*) and vitamin C influences cadmium poisoning (*25*), so nutritional status with regard to vitamins should be considered in order to obtain a comprehensive picture. Although the practical significance of human nutrition in relation to heavy metal toxicants is still to be determined, the research done to date suggests that the relation is important. In the meantime, however, purveyors of "health food" supplements are not waiting for the scientific data but are now marketing all manner of megadose vitamin and mineral combinations which are supposed to protect the buyer against all kinds of environmental stress. Overindulgence in such preparations might very well lead to problems of mineral toxicity or imbalance of another kind.

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