Interactions of Some Trace Element Nutrients and Xenobiotics Metabolism

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ABSTRACT

Requirements by animals and humans for dietary trace nutrients are often modified by interactions with other nutrients, with nonnutritive food components, with food additives and drugs, with environmental contaminants such as agricultural or industrial chemicals, and with natural xenobiotics such as mold toxins and toxicants in plants. Some selected examples of these interactions are reviewed briefly to illustrate various types of nutrient x xenobiotics interactions. For example, Zn requirements are increased by excessive dietary Ca, Cu or Fe, by dietary phytate, oxalate or (soluble) silicate, by Cd or Ga, by certain types of dietary fiber, and by ingestion of some kinds of clay. Certain types of mycotoxicoses (e.g., sporedesmin) and toxicoses caused by plant toxicants have been treated and even prevented by pharmacological levels of Zn. In ruminants, siliceous forages ingested contribute to soluble siliceous materials in rumen fluid that bind to Cu, Mn and Zn, thereby decreasing their bioavailability in the lower gastrointestinal tract. Deficiencies of Zn and other trace elements have been elicited by prolonged, unsupplemented total parenteral nutrition and by massive supplements of Fe. An increasing volume of biomedical literature has documented alterations in porphyrin biochemistry and metabolism associated with relatively low-level exposures to dietary and environmental toxicants and xenobiotics, including the trace elements Pb, As, Ga, Mn, Co, Ni and Cu. Some nutrient x toxicant interactions pose negative effects or overt adversity from nutritional supplementation that otherwise would be regarded as totally beneficial, e.g., Fe overload exacerbates the porphyria induced by dioxin, and Fe deficiency lends protection. Similarly, Zn supplementation exacerbated hyperbilirubinemia and other manifestations of hepatotoxicity in sheep caused by toxicants in the plant *Kochia scoparia*. Recently researchers at the University of Illinois caused As toxicosis in animals by providing excessive cysteine or ascorbic acid in

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diets containing normally used levels of arsenical compounds widely used as feed additives for swine and poultry. The levels of dietary Se that lead to symptoms of deficiency or of toxicity may be modified greatly by interactions with other nutrients or xenobiotics. Adequacy or inadequacy of trace element nutrients may be altered by xenobiotics in beverages such as tea, or by pharmaceuticals such as cimetidine or even non-prescription antacids containing soluble aluminum. Whether boron is a required nutrient or merely interacts with nutrients to provide benefits is a topic of current interest. Both requirements and tolerances of trace elements are modified by interactions with other nutrients and xenobiotics. Research to elucidate these interactions promises to improve animal and human health and to increase productivity of livestock.

INTRODUCTION

Some trace elements were recognized as nutrients because highly purified diets elicited symptoms that were corrected by addition of the element in question. But many were first regarded as nutrients only after pathologies in humans or impaired performance of livestock seemed related to diet and were corrected by dietary supplements. Some cases were related to interactions among dietary factors rather than overt lack of any specific element thought to be a nutrient. Some involved interactions with other known nutrients, causing increased need for the element not yet recognized as a nutrient; but other interactions involving non-nutritive dietary factors, especially xenobiotics, are now known to be numerous. These interactions, which complicate and modify not only the requirements for nutrients but also modify the tolerances of toxicants to which humans and animals are often exposed, have led to the recognition that "...today's thorniest...(nutritional and toxicological)...research problem...(is)...the fact that studies are necessarily carried out in controlled conditions, using only one chemical at a time, but man is always exposed at the same time or in succession to a mixture of chemicals, all with the opportunities for interactions between them..." (Garattini, 1983).

Some selected examples of these interactions are reviewed here briefly, merely to illustrate various types of nutrients x nutrient and nutrient x xenobiotic relationships that are now known to alter requirements for trace element nutrients and(or) tolerances of xenobiotics usually recognized as toxicants. Coverage here is neither comprehensive nor extensive, and the examples considered are not intended to reflect any category of priority or importance.

Xenobiotics

Since the beginning of life, living organisms have been exposed to natural elements and the chemical complexes that they form. This is true especially for heterotrophic organisms (animal life) that feed on autotrophic organisms (plant life) and thereby are exposed to a great variety of "body foreign" (i.e., non-nutritive, non-endogenous) and potentially toxic substances of plant origin. The term xenobiotic suggests merely that the substance does"...not occur naturally under favorable conditions in the biological objects

concerned" (Hathcock, 1982). Thus, even substances that are natural to plant or animal species may assume the characteristics of xenobiotics ("body-foreign") if they penetrate other species in a non-physiological way or in non-physiological amounts. "Xenobiotics thus are not necessarily abiotic in nature" (Hathcock, 1982; p.20). Human food and animal feeds are laden with hundreds or thousands of substances of plant or microbial origin that are non-nutrient, xenobiotic substances when absorbed, in addition to the feed additives, agricultural or industrial chemicals and environmental contaminants that are more widely recognized as xenobiotics. These non-nutritive, food-borne xenobiotics sometimes exert profound effects that characterize them as toxicants if strongly adverse or as medicinals (pharmaceuticals) if recognized as usually beneficial. Often these effects involve the distribution and metabolism of micro-nutrient trace elements. Numerous interactions between micronutrients (trace elements and vitamins) and macronutrient minerals and hazardous elements were reviewed definitively a few years ago (Levander and Cheng, 1980). Since then numerous reports and reviews have confirmed the view that "...the requirement for a nutrient or the hazard of a poison cannot be determined without taking into account how these substances might interact with one another." (Levander and Cheng, 1980; p.ix).

Nutrient x Nutrient Interactions

Among animal nutritionists and livestock producers it has been known for many years that requirements of specific micronutrients and especially trace elements are greatly modified by the dietary content, forms and bioavailability of other nutrients. For example, provision of trace elements to meet requirements for optimal growth or reproduction requires consideration of other minerals that might decrease availability at the intestinal level or increase requirements at the organ or cellular level (Underwood, 1977). This is illustrated classically by the well-known interactions among Cu, Mo and sulfate in the nutrition of ruminants. Other widely recognized interactions among micronutrients include Fe and ascorbate; Fe and vitamin A; Zn and vitamin A; Zn and vitamins B_{12}, C and E; Zn and Cu and Fe; Al and Ca, P, Mg and Al; and Se with several elements (Levander and Cheng, 1980; Hathcock, 1980, 1987; NRC, 1980).

Interactions with Toxic Elements

Improved tolerance of toxic elements through increased provision of nutrient trace elements has been shown in numerous cases (Underwood, 1977; Levander and Cheng, 1980; NRC, 1980). Well-known examples are improved tolerance of Pb by increased dietary Ca and(or) Fe, and modification of Pb toxicity at the tissue level by increased availability of Cu and Zn. Likewise, tolerance of Cd may be modified by dietary Ca, Cu, Se and(or) Zn; and tolerance of Hg can be modified by provision of Se or Ag. There are various examples where toxic, non-nutritive elements have been administered therapeutically to improve tolerance of micro-nutrient elements ingested at levels that are toxic, e.g., usage of As to alleviate chronic toxicosis from excessive Se (Klaassen et al., 1986).

SELECTED CASES

Siliceous plants and availability of trace elements

When consumed by ruminant animals, siliceous materials in plant products can be solubilized in the rumen fluid where ingesta are fermented and subsequently bind trace elements such as Cu, Mn and Zn, thereby decreasing availability not only to the microbes inhabiting the forestomach compartments but also to the host animal (Smith et al., 1971; Smith and Urquhart, 1975; Smith and Nelson, 1975). Soluble siliceous materials in drinking water or the diet have modified the uptake of minerals including toxic metals from the diet (Bruce et al., 1977). Moreover, contents of Cu, Mn and Zn in forages that are highly siliceous may be less available to herbivorous animals than similar amounts of these elements in non-siliceous forages (G. S. Smith, unpublished data). Although ruminants subsisting on siliceous plants excrete considerable quantities of siliceous substances in urine (sometimes resulting in siliceous urolithiasis), the effects on bioavailability and dietary requirements for trace elements such as Cu, Mn, and Zn have not been adequately examined in relation to other factors that also interact with these elements. Occasional reports that livestock on rangelands in the U.S.A. respond favorably to Zn supplements, even though forage content of Zn seems adequate to meet generally accepted standards of requirements, lend importance to further investigation of these relationships.

It is well established that bioavailability of dietary Zn is affected by levels and types of dietary fiber, and it seems established that ingestion of clay, as practiced by some people, may likewise bind Zn and other trace elements.

Hepatotoxicants, photosensitizations and interactions with zinc

Recently pithomycotoxicosis (facial eczema, a syndrome resulting from hepatic damage and photosensitization) in sheep on certain pastures in New Zealand was related to ingestion of the mycotoxin, sporedesmin. This syndrome was not only treated but also prevented by pharmacological levels of Zn, suggesting a vastly increased Zn "requirement" related to metabolic interactions involving this xenobiotic (Smith and Towers, 1985). Many hepatotoxicants cause derangement in metabolism of heme and other porphyrins, resulting in accumulation of bilirubin or porphyrin-type substances derived from chlorophyll and phylloerythrins, and these elicit photosensitization that often responds to Zn ointments applied topically. In recent experiments at New Mexico State University with sheep experiencing hyperbilirubinemia related to hepatotoxicosis from ingestion of the poisonous plant "beargrass" (*Nolina microcarpa*), benefits resulted from provision of Zn orally; but supplemental Zn severely exacerbated the hyperbilirubinemia and other signs of hepatotoxicosis related to ingestion of herbage from "kochia" (*Kochia scoparia*) (Rankins et al., 1988a, 1988b).

The production and metabolism of porphyrins and the relation of porphyrinopathies to low-level exposures of dietary or environmental xenobiotics and toxicants, including trace elements Pb, As, Ga, Mn,

Co, Ni, and Cu and involving direct relationships with Fe and Zn, were reviewed recently (NYAS, 1987). The enzymes, intermediates and products of porphyrin pathways are highly promising as biological markers because they are easily detected in available and accessible compartments. The complexities of porphyrias related to toxic xenobiotics and their interactions with trace elements are further illustrated by the fact that Fe overload exacerbates the porphyria induced by dioxin and Fe deficiency lends protection (NYAS, 1987; p. 136).

Interactions of cysteine and ascorbate with arsenicals

It is well known that cysteine, via glutathione, ameliorates the biochemical lesions caused by ingestion of excessive amounts of several trace elements. Furthermore, cysteine as precursor of glutathione and metallothioneins, participates in the conjugations and complexing of various organic and inorganic toxicants. Moreover, aside from these nutritional and metabolic interactions, cysteine at pharmacological levels chelates trace elements and toxic minerals directly in the gut, thereby decreasing their bioavailability and their toxicity. Thus there is the tendency to regard cysteine as generally beneficial, and less reason to regard cysteine as a xenobiotic and toxicant. The same can be said for ascorbic acid. Even at pharmacological levels, each is unlikely to be regarded with caution. In fact, poisoning with inorganic arsenic has been ameliorated by pharmacologic doses of cysteine or cysteine derivatives (e.g., dimercaptopropanol). But quite recently it was discovered that dietary cysteine, and also ascorbic acid, acting as reducing agents, produced overt, acute toxicosis in chicks and rats fed time-honored, beneficial levels of the organic arsenicals roxarsone and arsanilic acid in diets otherwise considered as practical and safe (Baker and Czarnecki-Maulden, 1987). In this case, the nutrient cysteine acted as xenobiotic-toxicant to cause detrimental effects from an otherwise beneficial xenobiotic feed additive.

Xenobiotics in Tea

Teas, coffee and other herbal brews are complex mixtures that usually contain caffeine, other methylxanthines, polyphenols and numerous complex organic compounds. It is less well recognized that some, and especially teas, contain various assortments of available trace elements, notably Al. Brews of tea and coffee are generally recognized as safe when used conventionally. Yet these widely used, mostly non-nutritive brews often exert profound effects on metabolic activities in organs and tissues, including the altered distribution and availability of numerous trace element nutrients (Greger and Lyle, 1987). Under what circumstances, if any, such interactions assume detrimental proportions has been poorly defined to date.

Cimetidine and aluminum antacids

Cimetidine is a histamine H_2-receptor antagonist that is used to treat human subjects with gastric or duodenal ulcers and other hypersecretory syndromes. It has become one of the most widely used drugs worldwide. Yet effects on trace element metabolism in humans have not been documented. Recent studies with laboratory animals suggested that tissue distribution of trace elements (Cu, Fe, Mn and Zn), and

even Ca and Mg, were markedly affected by both high and intermediate dosages of cimetidine, and these were accompanied by overt tissue damage and histopathology (Naveh et al., 1987).

Human subjects with chronic hyperacidity syndromes sometimes consume massive amounts of absorbable Al. Concern about accumulation of Al in brain tissue of Alzheimer's disease patients (Perl and Brody, 1980) may prove less important biologically than other, less dramatic, indirect effects of absorbed Al on the distribution and bioavailability of other trace mineral nutrients in varied syndromes less identified than Alzheimer's disease (Nutr. Rev., 1987).

Selenium in biology and medicine

Research on Se metabolism and the interactions of Se with nutrients, including trace elements, and xenobiotics has related Se usage and need to almost every nutrient and to many xenobiotics (Combs et al., 1987).

Boron

Evidence continues to accumulate that suggests boron may play an important role in the metabolism of minerals in animals and humans, with strong implications that boron has important interactions in the development and(or) course of osteoporosis (Nielsen, 1988). Two biologically active antibiotics, aplasmomysin and boromysin, contain boron. Whether boron is classed as a nutrient or as a xenobiotic seems, at this point, rather inconsequential. In either classification, the importance to animal productivity or to human health may likely relate to interactions with other nutrients, metabolites and(or) xenobiotics, thereby affecting primarily the requirements of other nutrients or the tolerance of other xenobiotics.

CONCLUSION

Animal and human requirements for most trace element nutrients have been established only within broad, general guidelines. They are altered by interactions with other nutrients and with numerous dietary and environmental factors, including xenobiotics. It is increasingly evident that requirements for, and tolerance of, the nutrient trace elements are modified, sometimes dramatically, by interactions that may blur ordinary classifications as nutrient or xenobiotic. The biochemical and metabolic changes that accompany some of the abnormalities resulting from severe deficiencies and toxicities promise important clues to benefits from development of these as biological markers. Research to elucidate the numerous interactions of trace element nutrients with other dietary and environmental factors likewise promises to improve animal and human health and to increase the productivity of livestock and other food-chain animals.

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