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Interactions between Selenium Compounds and Those of Mercury or Cadmium

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Two types of mechanisms are considered in this discussion of the interactions between compounds of selenium and those of cadmium or mercury: one based on a direct chemical reaction between compounds of these elements and the other based on metabolic changes induced by selenium administration and modifying the dose-effect relationship indirectly, without a reaction between selenium and the metallic compound. The second type of metabolic changes induced by selenium may explain why an increased selenium intake provides protection not only against methylmercury but also against the toxicity of methylated selenium compounds. A better understanding of the underlying mechanisms would help in assessing the importance of these interactions for man.

When discussing interactions of certain trace elements, two possibilities should be considered.

(1) The interaction can be direct, i.e., based on a direct chemical reaction between compounds of the elements in question. In the most simplified version, such an interaction could be of a "test-tube" type and occur without involvement of living matter. In other cases, a metabolic conversion of at least one of the interacting elements (compounds) would have to occur within the organism to make the interaction possible and/or a component of the living organism (such as certain protein molecules) would have to take part in the chemical reaction between the interacting trace-elements.

(2) Exposure to a certain trace element could modify the effects of the same or other element without their interacting directly at the molecular level. Such a modification could result, e.g., from metabolic changes, induced by a previous exposure and affecting the transport and metabolism of a certain toxic element, or affecting the ability of a target tissue to react to its presence. The necessity of a certain time interval for the development of the resistance can be considered as characteristic for some interactions of this type; however, this is usually apparent only in acute experiments, and could be obscured by chronic exposure to the interacting agents. Adaptation known to result from the exposure to certain trace elements belongs to this category.

The protective effect of selenite injection in animals exposed to an otherwise lethal dose of cadmium via inhalation was reported several decades ago (*1*). Since that time, substantial evidence has accumulated revealing that the administration of selenium compounds is highly effective in counteracting the toxicity not only of cadmium compounds but also of mercury and certain other metals. As discussed in previous detailed reviews of this problem (*2–5*), several mechanisms could be operating here, which could result, for example, in changed absorption of selenium and the metal involved (e.g., a compound of a different solubility in food and/or within the intestinal tract could be formed in the case of peroral administration) or in a change in their action and distribution in the organism and within target organs (e.g., due to a change of binding to proteins modifying at the same time both the distribution and the metabolic availability of selenium and of the metal involved). As regard selenium and inorganic mercury or cadmium compounds, administered parenterally, the latter case—a direct interaction of selenium, the metal involved, and proteins—seems

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to be the main mechanism responsible for the protective action of selenium (*6, 7*). It is important to note that with this type of reaction the protective effect, a decrease in toxicity, is connected with increased blood and blood plasma levels of mercury or cadmium and of administered selenium, as well as with increased retention of mercury and selenium in the organism (*3, 6, 7*). To get the effect, selenite and inorganic compounds of cadmium or mercury can be administered at the same time (*3, 6, 8*). However, relatively rapid metabolic conversion of selenite, probably its reduction, seems to be a prerequisite for this type of reaction (*9*).

A direct interaction between selenium and mercury might not be the mechanism responsible for the protective action of selenium in the case of methylmercury. Selenium could act here by influencing the sensitivity of the organism toward the toxic effects indirectly, through metabolic changes in target tissues, occurring before the exposure to the metal. In this respect it might be of interest that an increased selenium intake protects not only against the chronic toxicity of methylmercury (*10*) but also against the acute toxicity of dimethyl selenide (*11*).

An increased peroral intake of selenium as well as a single parenteral administration of selenite proved to be effective in decreasing dimethyl selenide toxicity. However, in contrast with the protection against inorganic mercury or cadmium, small amounts of selenite had to be given several hours before a toxic dose of dimethyl selenide, to have the protective effect developed (*11*). In this sense the situation is somewhat analogous to the protective effect of previous zinc or cadmium administration against the toxicity of a subsequent exposure to cadmium (*2, 4*).

Exposure to small amounts of mercury compounds is one of the factors which can remarkably increase the toxicity of methylated selenium metabolites (*12*) and this, as discussed previously elsewhere (*2*), could, of course, limit a safe use of selenium in the prevention of mercury toxicity. In this respect, it is important that dimethyl selenide toxicity can be controlled by increasing the level of previous selenium intake (*11*). In accordance with this, further experiments have shown that the risk of the previously described, dimethyl selenide-induced, lethal reaction in animals given compounds of selenium and mercury (*3, 12*) can be practically eliminated by pretreatment with smaller doses of selenite or by a gradual increase of selenium intake by food (*11*).

Knowledge of the mechanisms of the protective effects of selenium is obviously of importance for the discussion of two other essential questions, namely, the extrapolation of findings at high doses to lower exposure levels and the possible implications of selenium interactions related to human health. The effects of a selenium-deficient diet on inorganic mercury metabolism in rats, described more recently (*13*), and reported changes in selenium concentrations in tissues of men with an increased exposure to inorganic mercury (*14, 15*) suggest that selenium and inorganic mercury interact at physiological levels of selenium intake and in human exposure conditions. However, more research seems to be needed to deal with these questions in the case of methylmercury. Further experimental studies, e.g., with methylmercury exposure in selenium-deficient animals, should allow one to assess the interactions at low exposure levels and to evaluate the possibility of changes in selenium and methylmercury metabolism and effects under those conditions. Furthermore, it would be of particular importance to obtain information on selenium and mercury metabolism and effects in population groups in different parts of the world known to be exposed to different levels of methylmercury and to have different levels of selenium intake.

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