Effects of Simultaneous Low-level Dietary Supplementation with Inorganic and Organic Selenium on Whole-body, Blood, and Organ Levels of Toxic Metals in Mice

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Classical experiments have demonstrated that Se compounds protect against the toxicity of several toxic metals in acute experiments with simultaneous parenteral administration of high doses of Se and the toxic metal. Blood and organ levels of the toxic metals were increased, conceivably due to formation of inert Se complexes. Less is known about effects of long-term Se status on the toxicokinetics of toxic metals. Possible Se interactions in toxic metal biokinetics should therefore be studied at Se levels ranging from those just sufficient to avoid Se deficiency and up to those believed to be optimum in relation to antioxidative and other beneficial effects of Se. The toxic-metal exposure levels investigated should be similar to those occurring in human populations that are not occupationally exposed. To study interactions between Se and toxic metals at ultralow exposure levels, mice were fed semisynthetic diets containing different levels of Se. The mice were given ultralow doses of metal salts either as a single oral dose by stomach tube or as prolonged exposure in the drinking water. Diets with high or normal Se levels slightly, but nonsignificantly increased the whole-body retention (WBR) of Hg²⁺ and CH₃Hg⁺ compared to a diet low in Se. The dietary Se level was, however, without effect on the WBR of Cd²⁺ and Ag⁺ in single-dose experiments. During prolonged exposure, the diets fortified with Se increased the WBR of Ag⁺, had no effect on WBR of Hg²⁺, and reduced the WBR of CH₃Hg⁺ and Cd²⁺. During prolonged exposure, the diets fortified with Se reduced blood Hg²⁺ while organ levels were unaltered. Blood and organ levels of CH₃Hg⁺ were reduced or unaltered. Diets with added Se reduced blood and organ levels of Cd²⁺ but increased blood and organ levels of Ag⁺. The blood lead level was reduced by Se supplementation. These results are in contrast to those previously published for Se effects on the toxicokinetics of Cd and Hg compounds. The results indicate, that Se supplementation might be beneficial in populations exposed for extended periods to increased environmental levels of certain toxic metals, e.g., Cd, Hg and CH₃Hg. — Environ Health Perspect 102(Suppl 3):321-324 (1994).

Key words: diet, selenium, interactions, biokinetics, cadmium, inorganic mercury, organic mercury, silver

Introduction

Classical animal experiments have demonstrated that Se compounds may protect against the toxicity of several toxic metals — As, Cd, Pb, and inorganic and organic Hg. These experiments were mainly acute with simultaneous parenteral administration of high doses of Se and toxic metal; blood and organ levels of the toxic metals were found to be increased, conceivably due to formation of inert Se complexes. For reference to the original literature, see the extensive review by Nordberg et al. (1). The presently available knowledge about interactions between inorganic (i) and organic (o) species of Se and toxic metals in acute exposure experiments is briefly summarized in Table 1.

Less is known about effects of long-term Se status on the toxicokinetics of toxic metals. Possible Se interactions in toxic metal biokinetics should therefore be studied at Se levels ranging from those just sufficient to avoid Se deficiency to those believed to be optimum in relation to antioxidative and other beneficial effects of Se. The toxic-metal exposure levels investigated should be similar to those occurring in human populations that are not occupationally exposed.

The present study was aimed at investigating effects of nutritional Se status (i-Se and o-Se) on the toxicokinetics of toxic metals administered to mice at dose levels relevant for human exposures. Mice fed semisynthetic diets containing different levels of Se were given ultralow doses of metal salts labeled with γ-emitting isotopes. The optimum natural dietary source for Se is probably selenomethionine (SEM), as this methionine analog is absorbed almost completely, while selenite is absorbed almost completely, while selenate is absorbed only slowly.

| Metal | Effect |
|-------|--------|
| As    | i-Se decreases i-As toxicity |
| Cd    | i-Se decreases Cd toxicity; blood and organ Cd levels increase; Cd:Se = 1:1, Se is probably selenide |
| Pb    | Dietary i-Se decreases subchronic i-Pb toxicity; organ Pb and Se levels increase after combined exposure |
| i-Hg  | i-Se decreases i-Hg toxicity; blood and organ Hg levels increase; Hg:Se = 1:1, Se is probably selenide |
| o-Hg  | i-Se decreases o-Hg toxicity less efficiently than does i-Se; o-Se decreases i-Hg toxicity less efficiently than does i-Se; o-Se only marginally affects o-Hg toxicity |

The data were obtained mainly in acute experiments in rats exposed simultaneously to Se and toxic metals by parenteral routes. For reference to original publications, see Nordberg et al. (1).

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Table 2. Metal compounds, γ-emitting isotopes and dose levels used in the experiments.

| Isotope     | t1/2, days | Ψ-lines, keV | Dosage | Single dose, pg/kg | Drinking water, ng/l |
|-------------|------------|-------------|--------|------------------|---------------------|
| 109Cd       | 43 d       | 22, 88      | CdCl₂  | 1                | 8                   |
| 207Hg       | 47 d       | 279         | HgCl₂  | 1                | 6                   |
| 110mAg      | 253 d      | 658         | AgNO₃  | 10               | 60                  |
|             |            |             | PbCH₃COO| –                | 60                  |

For lead, a γ-emitting isotope was not available to us.

Materials and Methods

A total of 324 male B6C3F1 mice were fed modifications of a standard semisynthetic diet used in our laboratory. This diet contains dietary fibers (7% w/w Whatman cellulose) and all micronutrients. The energy contribution in the diet was: protein (caseinate) = 20%, lipid (coconut:soy 2:1) = 40%, carbohydrate mix = 40%. The Se content in ordinary mouse pellets used in our animal facility is about 50%. Certain natural Se species apparently have a very low bioavailability. Accordingly, the low-Se diet contained only SEM, and a mixture of SEM and selenium contributing identical amounts of Se was added to the two Se fortified diets as specified below.

Table 3. Effects of dietary Se levels on WBR (% of initial dose in single dose experiments, program metal in drinking water experiments) and organ distribution (µg/organ, pg/g blood) of metals after single dose or drinking water exposure.

| Se diet:         | Low          | Normal       | High         | Low          | Normal       | High         |
|------------------|--------------|--------------|--------------|--------------|--------------|--------------|
|                  | Single dose  | Drinking water | Single dose  | Drinking water | Single dose  | Drinking water |
|                  | WBR          | HgCl₂        | CH₃HgCl      | WBR          | HgCl₂        | CH₃HgCl      |
| Liver            | 54           | 6.05         | 80           | 4.89         | 83           | 6.36         |
|                  | 1838         | 6.89         | 1659         | 4.61         | 2234         | 6.44         |
| Kidneys          | 263          | 20.2         | 421           | 17.3         | 345          | 28.19         |
|                  | 1625         | 9.20         | 1873         | 8.23         | 1835         | 7.14         |
| Lungs            | 205          | 1.35         | 231           | 1.17         | 231          | 1.01         |
| Brain            | 177          | 0.85         | 219           | 0.49         | 216          | 0.79         |
| Blood            | 550          | 1.11         | 650           | 0.70         | 750          | 1.19         |
| Carcass          | 134          | 7.40         | 195           | 4.93         | 202          | 6.25         |
|                  | 14520        | 62.7         | 17320         | 38.5         | 140000       | 41.6         |

Metal compounds:

| WBR          | 0.6         | 14.4        | 0.8          | 64.8         | 0.6         | 6.4          |
|--------------|-------------|-------------|--------------|--------------|-------------|--------------|
| Liver        | 64.1        | 0.70        | 66.9         | 0.46         | 63.1        | 0.46         |
| Kidneys      | 88.7        | 0.72        | 92.3         | 0.52         | 68.8        | 0.53         |
| Lungs        | 110         | 0.048       | 73           | 0.062        | 100         | 0.092        |
| Brain        | 100         | 0.43        | 87           | 0.57         | 127         | 0.64         |
| Blood        | 0.003       | 0.003       | 0.003        | 0.002        | 0.002       | 0.002        |
| Carcass      | 14.3        | 1.084       | 18.1         | 0.57         | 15.5        | 0.67         |

For lead, a γ-emitting isotope was not available to us.

Toxicokinetic Analysis

All animals were counted in a whole-body counter (NaI well crystal Ø = 50 mm, 125 mm deep attached to a Searle 1195 R γ-counter) immediately after single-dose exposure, or at day 1 after starting the drinking-water exposure, then regularly for 14 days. After sacrifice, blood (drinking-water exposure) and organ concentrations were determined in the Searle 1195 R γ-counter. The detection limit was calculated for each isotope as the mean background value + 3 standard deviations based on 40 background countings. Blood lead levels were measured by graphite furnace AAS with Zeeman correction. Results are presented as medians and statistically compared.

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Table 4. Summary of results.

|   |   |   |
|---|---|---|
| i-Hg | Single dose | Se increases WBR by — 50% by increasing systemic deposition/retention |
|     | Drinking water | Se slightly and nonsignificantly reduces WBR, high Se increase kidney deposition |
| o-Hg | Single dose | Se increases WBR slightly, possibly by increasing uptake and/or reducing excretion |
|     | Drinking water | Se reduces WBR by — 50% by reducing systemic deposition/retention |
| Cd  | Single dose | Se insignificantly affects WBR and organ distribution |
|     | Drinking water | Se reduces WBR by reducing systemic deposition/retention |
| Ag  | Single dose | Se insignificantly affects WBR and organ distribution |
|     | Drinking water | Se increases WBR by increasing systemic deposition/retention |
| Pb  | Drinking water | Se slightly and non significantly reduces blood Pb |

Discussion

The results presented here are preliminary. To evaluate metal exposure levels that are relevant compared to normal or slightly increased human exposure levels, the experimental model employed metal doses at the borderline of the detection limits. As a result, many of the data sets obtained contain large variations both within and between groups exposed to the same toxic metal and different dietary Se levels. Although several rather large differences are not statistically significant, the combined results show a clear trend. The results are summarized in Table 4.

Drinking-water exposure is more relevant for human dietary metal exposure than single-dose exposures. In most of the drinking-water experiments reported here (Ag is an important exception), the result of increasing the dietary Se content by adding both i-Se and o-Se was a reduction of WBR and organ deposition of the toxic metals. The single-dose experiments gave results that are more in agreement with those from the classic investigations in rodents mentioned in the introduction. Thus, simultaneous parenteral administration of selenite and HgCl₂ resulted in extensively enhanced body retention of mercury, reduced urinary excretion, and enhanced organ deposition (2–7). Also, the protective effect of selenium compounds on organ toxicity of cadmium in acute exposure experiments is accompanied by enhanced cadmium deposition in these organs (1,3,8,9).

In conclusion, the results presented here indicate that effects of selenium compounds on the toxicokinetics of Cd and Hg compounds in human exposure would probably be different from effects predicted from previously published experimental animal studies, because Se reduced rather than increased toxic metal retention and organ deposition in exposure situations relevant for human exposure. The small effect of Se exposure on Hg kinetics observed in the present study is in accord with other recent results from our laboratory (10,11). As the present investigations used exposure levels for Se and toxic metals relevant for normal or slightly increased human exposure, the results indicate that Se supplementation might be beneficial in populations exposed to high environmental levels of toxic metals.
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