# Interrelationship Between Selenium and Specific Trace Elements[1] (35713)

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The biological interaction among specific nutrients is an accepted phenomenon (1). The importance of trace element interaction in eukaryotic cells lies in the belief that trace element antagonism arises from competition for active protein-binding sites (2). The metabolic relationship of specific trace elements to selenium is the main interest of our studies.

Experiments were carried out to investigate the metabolic interrelationship between selenium and sodium tellurate ($Te^{6+}$), sodium arsenate ($As^{5+}$), cadmium chloride ($Cd^{2+}$), zinc chloride ($Zn^{2+}$), sodium sulfite ($S^{4+}$) and sodium sulfate ($S^{6+}$). The pattern in the distribution and excretion of selenium in the presence of the above-mentioned trace elements varied from one to the other. Evidence indicates that there is at the site of injection a reaction between selenium and zinc or cadmium, but not between selenium and arsenic or tellurium. It appears that selenium prevents arsenic and tellurium from reaching target tissues.

*Methods.* Male rats weighing 100–150 g were used. Sodium tellurate ($Te^{6+}$), sodium arsenate ($As^{5+}$), cadmium chloride ($Cd^{2+}$), and zinc chloride ($Zn^{2+}$) were injected subcutaneously either as mixture with $^{75}$Se in the abdomen at one site, or the two trace elements were injected separately at two sites. The technique of injecting pairs of trace elements either as a mixture with $^{75}$Se at one site or separately at two sites has enabled us to observe if there was a reaction between the pairs of trace elements. All chemicals were reagent grade quality. Sulfite and sulfate were injected as a mixture with selenium at one site. All of the animals were injected with a single dose of $^{75}SeO_3{}^{2-}$ containing from 20 to 40 $\mu$Ci of radioactive selenium and sufficient nonradioactive $SeO_3{}^{2-}$ to equal 4.5 mg Se/kg of body weight. Following injection, the animal was placed in a glass metabolism cage[2] for 24 hr for the collection of urine, feces, and respiratory selenium. The reason for including the respiratory excretion of volatile selenium is because it is a very sensitive indicator of selenium metabolism. Procedures and methods used for the determination of the respiratory excretion of selenium and radioactivity have been described (3). The animals were decapitated at 24 hr and the tissues were assayed for $^{75}$Se along with the urine, feces, and the exhaled air. The results are expressed as radioactivity per g tissue weight. Exhaled air, urine, blood, and feces are expressed as percentage of the dose administered. It was assumed that the amount of $^{75}$Se present at a particular time in the experiment in each compartment was proportional to the amount of $^{75}$Se administered. This fraction (percentage of dose or counts per minute per g) was used as the dependent variable. The method of least squares was employed to predict percentage of dose or counts per minute per g from the concentration of Zn, Cd, Te or As. The significance of the deviation from the calculated line as an indication of the amount present in any one compartment with the change in the dose was estimated. Values of $P$: 0.01–0.05 were accepted as significant.

*Results. Zinc.* The administration of zinc chloride in molar ratios with selenium (Se/Zn) from *1:1* to *1:12* with single but not

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[2] Delmar Scientific Laboratories, Inc., Maywood, Ill.

with two injections caused a progressive decrease in the blood, urine and respiratory excretion of $^{75}Se$. There was a decrease in the fecal content of $^{75}Se$ with increases of zinc administration (Fig. 1). The liver, kidney, and large and small intestine showed a significant increase with the single injection (Table I). The total hide with a single injection but not with the two injections showed a significant increase in $^{75}Se$ content. This effect was not found in the entire hide itself but in the area of injection (*i.e.*, hide and muscle) which indicated that there was probably a reaction between selenium and zinc and not selenium and tissues which caused $^{75}Se$ to remain at the site of injection.

*Cadmium.* The administration of cadmium chloride in molar ratios with selenium (Se/Cd) from 1:0.5 to 1:4 with single but not with two injections caused a progressive decrease in the blood, urine, and respiratory excretion of $^{75}Se$ (Fig. 1). With both single and double injections the liver $^{75}Se$ content increased with the Cd dose (Table I). If selenium leaves the site of injection and enters the circulatory system, it tends to accumulate in the liver where perhaps a complex with cadmium is formed and deposited. In the hide with single injection, but not with the two injections, there was an increase in $^{75}Se$ content in the area (hide and muscle) of the injection. $^{75}Se$ combines or complexes with cadmium and remains at the site of the injection.

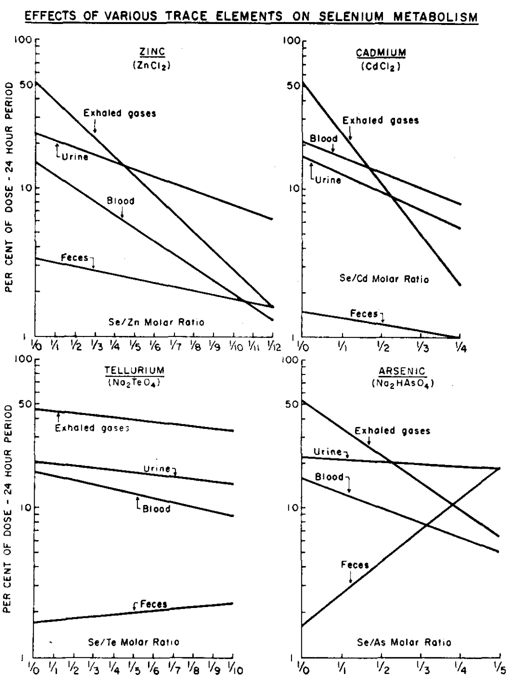


FIG. 1. Percentage of the $^{75}SeO_3^{2-}$ dose administered, 24 hr after injection, in the exhaled air, urine, whole blood, and feces of rats is shown in relation to the various molar ratios of selenium to Zn, Cd, Te, and As. The amount of $^{75}Se$ in each compartment was assumed to be proportional to the amount of $^{75}Se$ administered. With this fraction as the dependent variable, the method of least squares was employed to predict percentage of dose from the concentration of the various trace elements. *P*-0.01 to *P*-0.05 values were accepted as significant.

*Tellurium.* Sodium tellurate in molar ratios with selenium (Se/Te) from 1:1 to 1:10 in both single and two injections caused a slight but progressive decrease in the respiratory excretion of $^{75}Se$. In both modes of injections, there was a decrease in the selenium content in the urine and blood and a slight increase in the fecal content with increase in tellurium administration (Fig. 1). There was an increase in the $^{75}Se$ content in the liver, kidney, spleen, and testes, but not in the hide with increase in tellurium administration (Table I). There was no significant increase at the site of injection of $^{75}Se$ by either method. There was no evidence of complex formation between selenium and tellurium.

*Arsenic.* Sodium arsenate in molar ratios with selenium (Se/As) from 1:1 to 1:5 definitely caused a progressive decrease in the respiratory excretion of $^{75}Se$ whether the trace elements were administered together or separately, which is similar to tellurium (Fig. 1). Arsenic caused a reduction in the formation of volatile selenium probably by the complexing of administered selenium. Arsenic is excreted principally via the G.I. (gastrointestinal) tract (Table I). In experiments, where there were single and two injections, it was found that the selenium content of the stomach, and of the G.I. tract contents increased with an increase in arsenic administration. With increase in arsenic administration, the selenium content of the kidneys increased while that of the blood decreased in both single and two injections. Our results con-

TABLE I. Effects of Various Trace Elements on Selenium Metabolism.

For each pair of trace elements is tabulated the slope and intercept of the curve in relation to concentration of selenium to the other trace element. The *intercept* represents cpm $^{75}$Se per gram tissue or percentage of dose when no trace element was added (control) *i.e.*, 1:0, Se/trace element, molar ratio. The *slope* represents the rate of change of the cpm $^{75}$Se per gram tissue or percentage dose per unit change in molar ratio of trace elements; + indicates increase while — indicates decrease; tissue results = cpm/g of tissue wt $\times 10^{-3}$; $N$ = number of experiments; stomach and intestinal contents = % of the dose administered; the significance of the deviation from the calculated line is Sig column. Selenium injected without other trace elements served as controls. M* = either Cd, Zn, Te, and As.

| | Injection Site | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Moles Se/Cd | | | | | | Moles Se/Zn | | | | | |
| | Single 1:0.5 to 1:4 ($N$ = 5) | | | Double 1:1 to 1:3 ($N$ = 4) | | | Single 1:1 to 1:12 ($N$ = 12) | | | Double 1:1 to 1:10 ($N$ = 5) | | |
| | Slope | Intercept | Sig | Slope | Intercept | Sig | Slope | Intercept | Sig | Slope | Intercept | Sig |
| | Cadmium | | | | | | Zinc | | | | | |
| Kidneys | + 0.86 | 50.1 | Nil | — 1.15 | 53.7 | Nil | + 7.73 | 42.2 | —[a] | + 3.7 | 61.5 | Nil |
| Liver | + 20.93 | 68.6 | —[b] | +22.58 | 69.8 | Nil | + 5.40 | 51.8 | —[b] | + 4.21 | 70.2 | Nil |
| Small intestine | + 2.58 | 11.5 | Nil | + 1.33 | 15.7 | Nil | + 2.51 | 9.2 | —[a] | + 1.06 | 13.5 | Nil |
| Large intestine | + 3.11 | 9.5 | —[b] | + 0.69 | 11.2 | Nil | + 1.43 | 9.2 | —[a] | + 0.79 | 12.6 | Nil |
| Stomach contents | + 0.294 | 0.848 | Nil | — 0.019 | 0.153 | Nil | + 0.005 | 0.123 | Nil | 0.010 | 0.175 | Nil |
| Intestine contents | + 1.190 | 1.577 | Nil | + 0.012 | 1.675 | Nil | — 0.016 | 1.671 | Nil | — 0.137 | 2.385 | Nil |
| Total | + 1.219 | 1.677 | —[b] | — 0.23 | 1.764 | Nil | — 0.002 | 1.708 | Nil | 0.071 | 2.161 | Nil |
| Carcass | + 4.89 | 7.2 | —[b] | + 1.01 | 7.9 | Nil | + 1.29 | 5.6 | —[a] | + 0.28 | 7.78 | Nil |
| Hide, total | + 9.7 | 20.9 | —[b] | | | | + 2.19 | 0.76 | —[a] | | | |
| M*–Se site[c] | +662.0 | 12.6 | —[c] | | | | +81.64 | 192.2 | —[b] | | | |
| Se site | | | | +12.04 | 35.3 | Nil | | | | +18.44 | 74.25 | Nil |
| Muscle, total | + 3.8 | 2.2 | —[b] | | | | +20.78 | 4.5 | —[b] | | | |
| M*–Se site | +668.4 | — 4.1 | —[b] | | | | +29.29 | 14.69 | —[a] | | | |
| Se site | | | | + 8.57 | 22.7 | Nil | | | | + 1.32 | 39.85 | Nil |

TABLE I. (continued)

| | Moles Se/Te | | | | | | Moles Se/As | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1:1 to 1:10 ($N = 5$) | | | 1:1 to 1:10 ($N = 3$) | | | 1:1 to 1:5 ($N = 7$) | | | 1:1 to 1:5 ($N = 7$) | | |
| | Tellurium | | | | | | Arsenic | | | | | |
| Kidneys | +11.79 | 44.7 | —[a] | +11.66 | 44.5 | —[a] | +98.14 | 66.7 | —[c] | +68.7 | 98.9 | —[c] |
| Liver | +18.91 | 48.4 | —[c] | +20.67 | 43.7 | —[a] | + 2.79 | 51.6 | Nil | + 2.06 | 52.6 | Nil |
| Small intestine | — | — | | + 0.08 | 10.8 | Nil | + 1.32 | 10.8 | —[b] | + 1.05 | 10.8 | Nil |
| Large intestine | 0.52 | 9.1 | —[b] | + 0.20 | 8.9 | Nil | + 4.92 | 7.2 | —[c] | + 3.73 | 8.3 | —[a] |
| Stomach contents | + 0.044 | 0.137 | —[a] | + 0.054 | 0.104 | —[b] | + 0.208 | 0.014 | —[b] | 0.102 | 0.334 | Nil |
| Intestine contents | − 0.013 | 1.242 | Nil | + 0.205 | 1.060 | Nil | + 2.018 | 1.857 | —[b] | 1.39 | 0.75 | —[a] |
| Total | + 0.023 | 1.43 | Nil | + 0.241 | 1.509 | Nil | + 2.87 | 0.925 | —[c] | + 1.45 | 1.26 | —[a] |
| Carcass | + 0.08 | 6.6 | Nil | + 0.25 | 6.0 | Nil | + 0.02 | 5.9 | Nil | + 0.06 | 6.7 | Nil |
| Hide | | | | | | | | | | | | |
| M*–Se site | − 0.93 | 37.3 | Nil | | | | + 1.30 | 25.9 | Nil | | | |
| Se site | | | | + 3.56 | 35.5 | Nil | | | | + 0.23 | 33.4 | Nil |
| Muscle | | | | | | | | | | | | |
| M*–Se site | − 0.17 | 12.17 | Nil | | | | − 0.25 | 13.2 | Nil | | | |
| Se site | | | | + 3.75 | 11.84 | —[b] | | | | + 2.76 | 27.0 | Nil |

Significance: [a] $0.05 > p > 0.02$; [b] $0.10 > p > 0.06$; [c] $p < 0.01$.

firm those of Ganther and Baumann (4) and Parizek (5, 6) that the administration of cadmium decreased the excretory selenium via the G.I. tract, urine and respiratory tract while arsenic caused an increase in the excretion of selenium via the G.I. tract.

*Sulfur.* The administration of single injections of sodium sulfite in molar ratios with selenium (Se/S) from 1:1 to 1:5 and sulfate 1:1 to 1:48 caused no significant change in the metabolism of selenium due to the presence of sulfur compounds.

*Discussion.* Selenium can prevent the selective and highly lethal effects of cadmium on the gonads, placenta, and mammary glands of the rat. It causes a decrease in the transmission of cadmium or bivalent mercury from the maternal organism into the fetus, the milk, and the pups, by increasing the retention of cadmium or bivalent mercury (7). Conversely, mercury or cadmium have analogous effects on the passage of selenium from the maternal organism to the fetus, milk, and sucklings. It is believed that selenium reacts with cadmium or mercury in the organism in such a way to alter the biological effects of these metals, as well as change the distribution of selenium in the organism. Parizek (7) has discussed the detoxifying effects of selenium in relation to selenium as an essential nutrient.

In our studies the over-all effect of zinc on selenium metabolism was that when Se and Zn were administered as a mixture, part of selenium remained at the site of injection. This caused a decrease in the amount of selenium metabolized which was reflected in the respiratory excretion, blood, and urine content. With two injections, a larger amount of selenium was metabolized, the normal respiratory excretion taking place with a significant increased excretion via the G.I. tract. Zinc caused no significant increased deposition of selenium either in the liver or kidneys. The increase in $^{75}$Se content in the carcass was probably due to the increase at the site of injection in the single-injection experiments. Contrary to our findings, Parizek was unable to detect any effect of equimolar concentrations of zinc on selenium metabolism (6).

With a single injection of cadmium, less $^{75}$Se reached the circulation but remained at the site of injection. That which reached the blood stream was deposited in the tissues, and the ability to form volatile selenium compounds was reduced.

With tellurium the amount of selenium excreted in the respiratory gases and urine and that present in the blood was reduced while there was an increase in $^{75}$Se in the liver, kidney, muscle and hide. There was no significant difference from the controls in the elimination of $^{75}$Se by way of the G.I. tract.

There was no marked difference in the quantitative metabolism of selenium between the single and two injections of selenium and arsenic. With arsenic there was no evidence of complexing with selenium at the site of injection as was found with cadmium and zinc.

The administration of sodium sulfate or sodium sulfite had little or no effect on selenium exhalation or tissue distribution.

The findings that both arsenic and tellurium affect the normal metabolism and excretion of selenium may be explained in part by the concept proposed by C.H. Hill (1) that trace elements with similar electron structures such as $Se^{4+}$, $As^{3+}$, and $Te^{4+}$ will be biological antagonists. Changes were brought about in the normal pattern of selenium metabolism by arsenic and tellurium in both the single- and two-site injection experiments. In the zinc and cadmium experiments, where the trace elements have different orbital electron distribution from selenium, it was found that selenium metabolism was altered only when the trace elements were administered as a mixture (single injection). Therefore, the effect of zinc and cadmium on selenium metabolism cannot be explained on the basis of electron structure. Since the effect of zinc and cadmium on selenium metabolism took place only with single injections, there appeared to be a reaction between selenium and zinc and cadmium ions, whereas arsenic and tellurium affected selenium metabolism by preventing selenium perhaps from reaching a target tissue or site.

*Conclusion.* The pattern in the distribution and excretion of selenium in the presence of other trace elements varied from one trace element to the other and with the mode of injection. The precise mechanism by which $Te^{6+}$, $As^{5+}$, $Cd^{2+}$, or $Zn^{2+}$ alter the metabolism of $Se^{4}$ is not known. Whether the resulting effect between two trace elements is due to competition for an active site on a biologically active compound, or competition for an active transport carrier across a cell membrane, or masking by complexing remains a matter of pure speculation. It has been shown that certain trace elements have a significant effect on the normal metabolism and excretion of selenium. Evidence suggests that there is a reaction between selenium and zinc and cadmium, while selenium appears to prevent arsenic and tellurium from reaching target tissues.

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