The Absorption and Tissue Distribution of Selenium from High-Selenium Broccoli Are Different from Selenium from Sodium Selenite, Sodium Selenate, and Selenomethionine As Determined in Selenium-Deficient Rats

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The absorption, tissue distribution, and body retention of selenium (Se) from hydroponically grown high-selenium broccoli were determined in rats. Animals were fed a Torula yeast based diet with no Se or supplemented with 0.1 mg Se/kg diet added as sodium selenate (controls) for six weeks. Selenium-deficient animals were then repleted with Se (0.1 mg/kg diet) supplied as either sodium selenate, sodium selenite, selenomethionine (SeMet), or high-Se broccoli. High-Se broccoli was grown hydroponically and contained 28 mg Se/kg (dry wt). Gross absorption of Se and absorption adjusted for urinary excretion of Se from high-Se broccoli were significantly lower than from other sources. Sodium selenite, sodium selenate, and SeMet were similarly effective in restoring most measures of Se status; high-selenium broccoli was much less effective. However, Se from high-selenium broccoli was nonsignificantly different from the other forms in restoring kidney and plasma Se concentrations. Similarly, Se from high-selenium broccoli was less effective than the other forms of Se in restoring glutathione peroxidase enzyme activity. We conclude that Se from high-selenium broccoli is absorbed, distributed, and retained in a different manner than Se from sodium selenite, sodium selenate and SeMet. These differences are probably because the metabolic pathway used by Se from high-selenium broccoli is different from the pathways used by the other forms of Se utilized in this study.

Keywords: *Selenium; broccoli; absorption; tissue distribution; sodium selenate; sodium selenite; selenomethionine*

The essentiality of selenium (Se) was first established because of the ability of supplemental Se to prevent several disease conditions in domestic and laboratory animals (National Research Council, 1983). Later Se was shown to be at the catalytic site and an essential component of the enzyme glutathione peroxidase (GSH−Px) (Rotruck et al., 1973). Presently, the recognized functions of Se include function in numerous selenoproteins (Burk and Hill, 1993), prevention of several diseases in animals (National Research Council, 1983), prevention of Keshan's disease in humans (Chen et al., 1981), and perhaps, prevention of cancer in humans (Clark et al., 1996). A Recommended Dietary Allowance (RDA) of 55 and 70 μg/day for women and men, respectively, has been established by the National Research Council (1989). Although most North Americans consume this much Se, supplemental Se consumed in amounts of up to 200 μg/day may have beneficial effects on cancer prevention (Clark et al., 1996).

Selenium may be metabolized by multiple pathways, and the metabolic pathway determines the ultimate disposition of, and consequently, the functions and benefits of Se. Selenium as hydrogen selenide can be incorporated into selenoproteins by a unique pathway that involves production of selenocysteine (SeCys) and incorporation of SeCys into the polypeptide chain by using UGA as the insertion codon (Burk and Hill, 1993). Hydrogen selenide also may enter the excretory pathway and become mono-, di-, or tri-methylated (Vadhanavikit et al., 1993); the trimethylated form is the main excretory product and is found in urine (Vadhanavikit et al., 1993).

The form in which Se is consumed determines the pathway that is followed. For example, Se in the form of selenomethionine (SeMet) is less efficacious than selenite in preventing cancer (Ip et al., 1991), and this difference is explained by the theory that methyl selenol is the form of Se active against cancer, and selenite is more easily metabolized to this form than is SeMet. Some foods, such as high-selenium garlic, contain Se in the form of Se-methyl selenocysteine (SeMC) (Cai et al., 1995). This form of Se is initially metabolized to methyl selenol, and that may explain the large cancer-preventative effect of high-selenium garlic (Ip and Lisk, 1995).

Consumption of broccoli has substantial health benefits unrelated to selenium (Doll and Peto, 1981). Broccoli grown in the presence of Se can accumulate substantial amounts Se (Banuelos and Meek, 1989) and, like garlic, also contains Se as SeMC (Cai et al., 1995). Consequently, it is possible that the health benefits of broccoli may also be improved by the presence of high concentrations of Se. However, very little is known of how the body absorbs, distributes, and metabolizes Se from broccoli. Such information is especially important

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because Se in broccoli, as SeMC, is very different from selenomethionine (SeMet), the primary form found in wheat and meat (Cai et al., 1995). (Wheat and meat are the main sources of Se in the diet (Levander, 1986).) Therefore, the purpose of this study was to determine the absorption, retention, and distribution of Se in broccoli as compared to the forms of Se that have been studied more often—sodium selenite, sodium selenate, and SeMet.

MATERIALS AND METHODS

Experimental Design. The absorption, tissue distribution, and body retention of Se from high-selenium broccoli were determined in rats made Se-deficient by feeding Torula yeast-based diets until measures of Se status were low. Rats were then repleted with Se by feeding diets that contained adequate concentrations of Se that came from different sources, including broccoli. Selenium status was then assessed by measuring status indicators including organ Se concentrations and glutathione peroxidase (GSH−Px) activities. Status indicators in rats fed high-selenium broccoli were compared to status indicators in animals fed sodium selenate, sodium selenite, and SeMet, and to control animals that were fed a Se-adequate diet the entire time.

Animals and Diets. The study used 96 male, Sprague Dawley rats (SASCO, Madison, WI) purchased as weanlings weighing 40−50 g. Seventy-six animals were immediately fed a Se-deficient diet (Torula yeast plus 3.5 mg/kg menadione, Harlan Teklad, Madison, WI, TD86298) and the remaining 22 were fed a control diet containing 0.1 μg/g Se as sodium selenate (reagent grade, 98% purity; Aldrich Chemicals, Milwaukee, WI). At the end of the six-week depletion period, four rats from the control group and four rats from the depletion group were killed to ascertain that the Se-deficient diet had induced a depleted Se status. Animals were maintained in environmentally controlled rooms in stainless steel cages with ad libitum access to deionized water.

Animals depleted of Se were randomly allocated to four groups of 18 animals each. Diets for the four groups were as follows: (1) high-selenium broccoli diet that contained 0.1 μg of Se from broccoli/g of diet; (2) sodium selenite diet that contained 0.1 μg of Se as sodium-selenite/g of diet (reagent grade, 98% purity; Aldrich Chemicals, Milwaukee, WI); (3) sodium selenate diet that contained 0.1 μg of Se as selenate/g of diet (reagent grade, 98% purity; Aldrich Chemicals, Milwaukee, WI); and (4) SeMet diet that contained 0.1 μg of Se as L-SeMet/g of diet (reagent grade; Sigma, St. Lois, MO). All four diets contained the same amount of broccoli, but the broccoli came from different sources (see below). The analyzed selenium contents of the diets (μg of Se/g of diet; means ± std dev) were as follows: Se-deficient, 0.015 ± 0.001; high-Se broccoli, 0.10 ± 0.01; sodium selenite, 0.10 ± 0.04; sodium selenate, 0.11 ± 0.05; SeMet, 0.09 ± 0.02.

Broccoli Production. All diets were formulated to contain 3.62 g of broccoli/kg of diet. The Se-deficient, sodium selenite, sodium selenate, and SeMet diets used low-Se broccoli that contained 6.6 ng of Se/g (dry wt), whereas the high-Se broccoli diet used broccoli with a Se concentration of 27.6 μg of Se/g (dry wt). Broccoli was grown hydroponically (Vanderpool and Johnson, 1992) in a greenhouse; broccoli was germinated in soil-free medium and transferred at the first leaf stage to three gallon square containers of nutrient solution. Mineral contents of the solutions were maintained by daily nutrient additions; distilled water was added daily to maintain nutrient solution volume. Air was bubbled through each of the containers by using an aquarium pump. Broccoli heads and leaves were harvested and lyophilized when the heads were mature.

Sample Collection. After an overnight fast, rats were anesthetized (87 mg/kg ketamine and 13 mg/kg xylazine) then euthanized by exsanguination. Liver, liver cytosol, muscle, kidney, plasma, and erythrocytes were analyzed for Se concentration. Liver cytosol and whole blood were analyzed for GSH−Px activity by using the coupled enzyme method of Paglia and Valentine (1967).

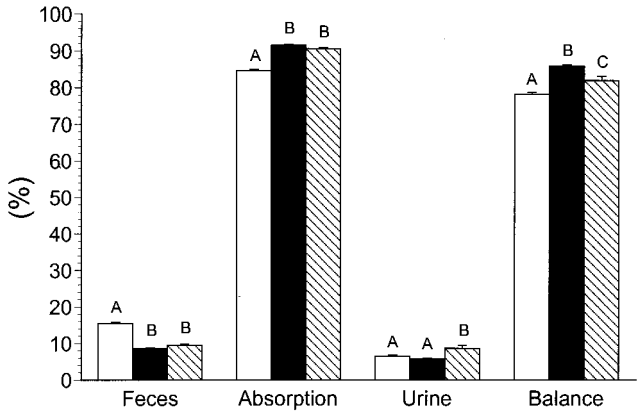

Figure 1. Effect of source of Se on the percentage of dietary Se in the feces, absorbed, excreted in the urine, and retained by rats (true absorption/balance).

Se was analyzed by hydride generation atomic absorption spectrometry (HGAAS) after samples were digested in nitric acid (Finley et al., 1996). Selenium analyses were done in duplicate; the run to run coefficient of variation averaged 6.9%. Quality control was maintained by using normal range plasma controls (Utak Laboratories, Inc., Valencia, CA; expected Se concentration of 98−125 ng/mL, analyzed concentration of 127 ± 2.65 ng of Se/mL).

Absorption and Balance. To determine whether differences in distribution of Se from different sources were caused by differences in absorption, a balance study was conducted with 27 male rats (weanling, Sprague−Dawley). Animals and diets were identical to animals and diets in the above study, only the sources of Se were sodium selenate, SeMet, and high-selenium broccoli. Sodium selenite and control diets were not fed. Animals were fed their respective diets for three weeks and then put into metabolism cages for an additional week. Complete urine and fecal collections were made while in the metabolic cages so that gross and net absorption of Se could be calculated.

Statistics. Data were analyzed by a two-way analysis of variance (ANOVA) that included Se source and day of repletion in the model. Individual comparisons were done by calculating all pairwise comparisons by using Tukey's contrasts (SAS/STAT, SAS Institute, Cary, NC). Differences were considered significantly different if $p < 0.05$. An analysis of absorption data found a difference in absorption for Se from broccoli, and Se from selenate and SeMet. Consequently, repletion data for Se from broccoli were adjusted to reflect the Se concentrations and GSH−Px activities that might have been if absorption were the same for broccoli. Figures show both adjusted and unadjusted values; statistical comparisons were only made with adjusted values.

RESULTS

Se Depletion. Selenium status was substantially depressed in rats fed the torula yeast diet, as compared to animals fed the control diet. Selenium concentrations in depleted rats, as a percent of controls, were 23.8% in muscle, 6.8% in liver, 20.3% in kidney, and 17.2% in erythrocytes. The activity of GSH−Px in liver cytosol was 1.3% of controls, and whole-blood activity was 20.0% of controls.

Absorption of Se from High-Se Broccoli and Other Sources. Food intake and daily Se intakes were not different between the treatments; Se intake averaged 1796 ng/d. Figure 1 shows the effect of dietary source of Se on percentage of dietary Se found in the feces and urine, percent apparent absorption, and percent absorption corrected for urinary Se (balance).

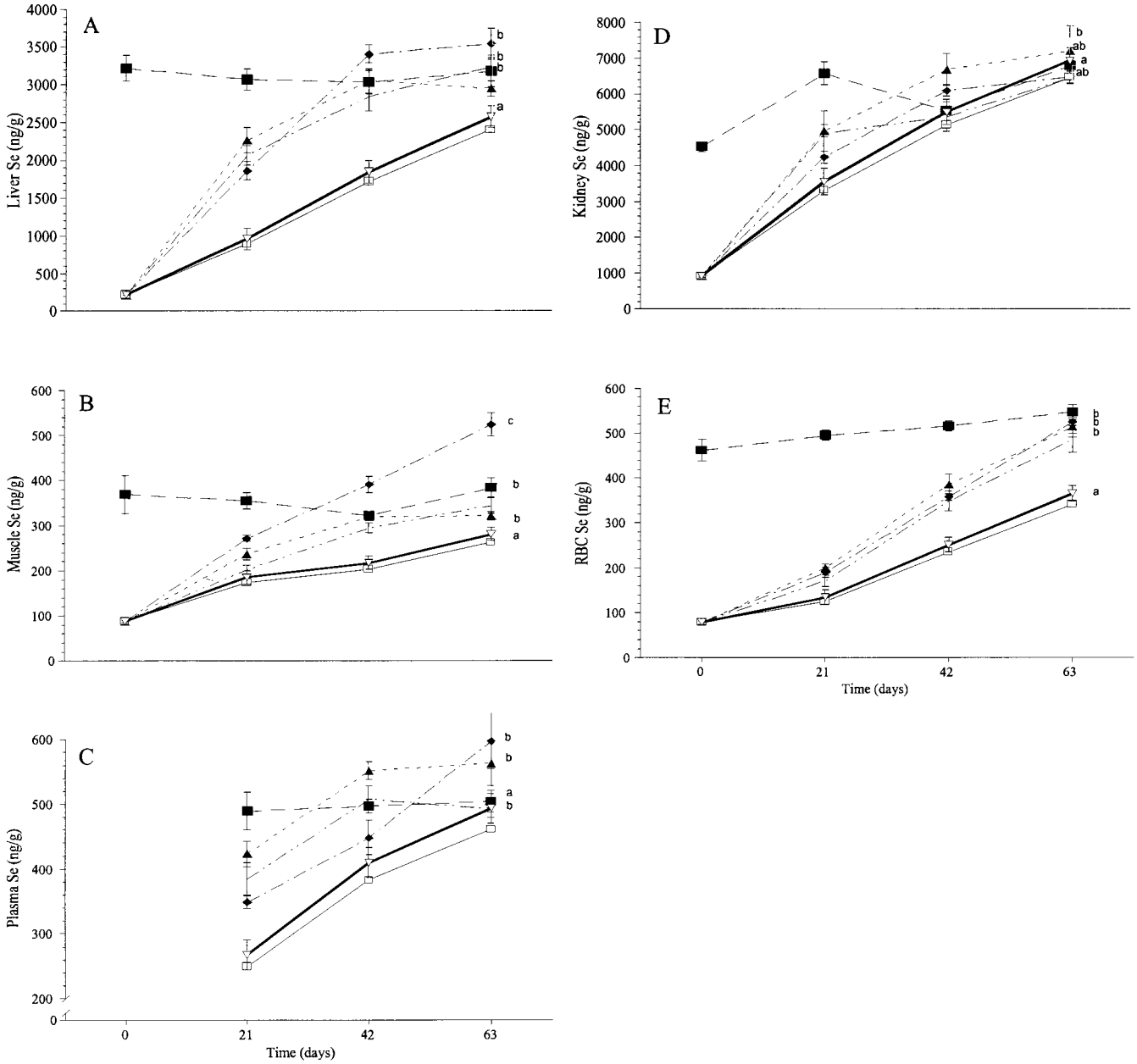

Figure 2. Effect of source of Se on the restoration of Se concentration in the tissues of rats fed a low Se diet for 6 weeks. Rats fed a torula yeast diet for 6 weeks were re-fed a diet adequate in Se (0.1 mg Se/kg) with Se supplied as sodium selenate (— • • —), sodium selenite (▲), selenomethionine (♦), high-Se broccoli uncorrected for absorption (□), or high-Se broccoli, corrected for absorption (▽). Control animals (■) were fed a diet containing 0.1 mg Se/kg (Se as selenate) for the entire experiment. Values are the mean of six animals ± the standard error of the mean. Repletion of Se is shown for liver (A), muscle (B), plasma (C), kidney (D), and erythrocytes (E).

Apparent absorption of Se was significantly less ($p < 0.05$) for broccoli (85%) than for sodium selenate (91%). Absorption of Se from SeMet was not significantly different from sodium selenate.

Urinary excretion of Se was significantly different ($p < 0.05$) between high-selenium broccoli and sodium selenate diets, and between the SeMet and sodium selenate diets; however, it was not different between the high-selenium broccoli and SeMet diets. True absorption that was adjusted for urinary excretion was significantly different ($p < 0.0001$) for all three dietary groups, with the lowest true absorption being for high-selenium broccoli and the highest being for SeMet.

Se Repletion. Body weights were not affected ($p > 0.05$) by dietary Se source during the repletion period.

Selenium repletion in the liver (Figure 2A) showed a pattern observed in several other organs. The restoration of liver Se was not significantly different in rats fed sodium selenate, sodium selenite, and SeMet, but all of these treatments resulted in significantly higher Se concentrations than in rats fed high-selenium broccoli. Sodium selenate, sodium selenite, and SeMet restored liver Se in a pattern that suggested saturation of liver Se concentrations beginning around day 42. Conversely, Se from broccoli continued to increase Se in liver in a linear manner throughout the study.

Restoration of Se in muscle is shown in Figure 2B. Sodium selenate and sodium selenite were not significantly different in their ability to restore muscle Se, but rats fed SeMet accumulated Se in the muscle at a

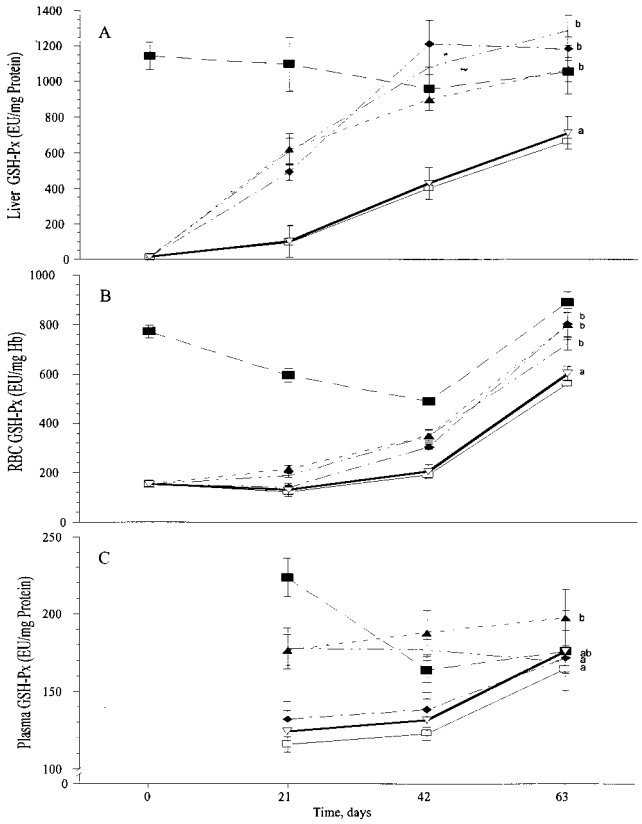

Figure 3. Effect of source of Se on the restoration of glutathione peroxidase in tissues. See Figure 1 for description of experimental methods and legend. Repletion of GSH−Px activity is shown for liver cytosol (A), whole blood (B), and plasma (C).

significantly ($p < 0.05$) faster rate than the other treatment groups. High-selenium broccoli restored Se in the muscle at a significantly slower rate than all other treatments.

Sodium selenate, sodium selenite, and Se from high-selenium broccoli repleted Se in plasma (Figure 2C) in a manner that suggested saturation beginning around day 42, whereas Se from SeMet continued to accumulate linearly. When Se from high-selenium broccoli was unadjusted for absorption, it restored plasma Se at a rate significantly less than all other treatment groups. However, when the concentration of Se from broccoli was adjusted for absorption, after 63 days the concentration of Se in plasma was not significantly different from any other treatment.

The kidney (Figure 2D) was different from other tissues in that there was little difference between the various forms of Se in their ability to restore Se concentrations. After 63 days, there were no significant differences in kidney Se concentration between any of the sources, and the rate of Se repletion was only significantly different for sodium selenite and high-selenium broccoli. Because of the long half-life of erythrocytes, repletion was minimal the first 21 days (Figure 2E); thereafter repletion continued in a linear manner until the end of the study. After 63 days, all sources of Se had repleted erythrocyte Se equally, except high-selenium broccoli, which was approximately 62% of the other sources.

Repletion of classical GSH−Px activity in liver cytosol (Figure 3A), whole blood (Figure 3B), and extracellular GSH−Px activity ($GSH-Px_{ec}$) in plasma (Figure 3C) occurred in a manner similar to repletion of Se concentrations in these tissues. Se from high-selenium broccoli was the least effective form for restoring GSH−Px activity in all tissues.

DISCUSSION

Supplemental intake of Se may have benefits to human health and well-being (Clark et al., 1996); however, the benefits of Se depend on the form in which it is ingested (Vadhanavikit et al., 1993). For supplemental Se to be beneficial, it must have certain attributes. First, it must have health benefits; for most people in Western countries, this primarily means it must be efficacious against cancer (Clark et al., 1996). Second, Se is a very toxic element (Levander, 1986) and the supplemental form of Se must be relatively nontoxic, which means it should not accumulate excessively in the body. Finally, Se is needed for the activity of selenoproteins (Burk and Hill, 1993), and the supplemental form of Se must be able to incorporate into selenoproteins when Se intake is deficient.

High-Se garlic has a great protective effect against mammary cancer (Ip and Lisk, 1995) and it does not accumulate in tissues as well as Se consumed as a salt or as selenomethionine (Ip and Lisk, 1994) but the health benefits of garlic will always be constrained by the negative social connotations. Because broccoli does not have the negative social impact of garlic, because it is a common vegetable eaten by many consumers that has many health benefits unrelated to Se, and because the Se in broccoli may be in the same chemical form as Se in garlic (Cai et al., 1995), high-Se broccoli may be a better way of supplementing dietary Se. This report shows that high-Se broccoli meets two of the above criteria for a good supplemental form of Se: It does not accumulate in most tissues to the same extent as SeMet or Se from salts, but it is available for incorporation into selenoproteins when dietary Se is deficient.

The only previous study with results comparable to the present study fed weanling rats Se as high-selenium garlic (Ip and Lisk, 1994). It should be noted that they used dietary Se concentrations well in excess of the dietary requirement, and that they did not first deplete animals of Se. Despite these differences, the commonality between that study (Ip and Lisk, 1994) and the present study was that Se fed as either high-Se garlic or high-Se broccoli tended to accumulate less in most tissues than Se fed as SeMet. Contrary to results of the present study, however, was that Se from high-selenium garlic accumulated more in muscle tissue than Se from selenite (Ip and Lisk, 1994).

A supplemental source of Se should be relatively nontoxic and not accumulate in tissues, but when dietary Se is limiting, it should also be able to replenish the Se pool used for selenoprotein synthesis. Two results of the present study suggest that high-selenium broccoli is able to supply Se for this purpose. First, GSH−Px activity in liver cytosol and erythrocytes increased following supplementation with high-Se broccoli, although the increase was not as rapid as with other sources. Second, Se accumulation in the kidney was not significantly different for any of the treatment groups after 60 days. However, rats fed high-Se garlic without first being depleted of Se (Ip and Lisk, 1994) accumulated less Se in the kidney than from selenite or SeMet. This implies that when dietary Se is deficient, pathways exist that allow Se in the form supplied by garlic and broccoli to be metabolized into a form

retained in the tissues. However, when dietary Se is high, metabolism may not allow retention in this tissue.

Results of both rat studies were different from those obtained in a recent human study (Finley et al., 1995). Healthy young men were fed stable ^{74}Se as sodium selenate and ^{82}Se intrinsically incorporated into hydroponically grown broccoli. A single isotope dose was given, and Se absorption was not different between sodium selenate or Se from broccoli; however, urinary excretion was much greater for selenate. Consequently, more Se from broccoli was retained than from sodium selenate, but despite this greater retention of Se from broccoli, less Se from broccoli was found in the plasma (Finley et al., 1995). It should be noted, however, that broccoli fed in the human study was enriched in Se isotope, but the total concentration of Se in the broccoli was similar to that in normal broccoli, and consequently, it is possible that the Se may have been in a different chemical form. Current studies are attempting to determine if the chemical form of Se in broccoli changes as the Se concentration in the plant increases.

The present study adds to a growing body of information that shows the retention and distribution of Se from foods depends on the food that is fed. Most of these studies have compared the ability of different forms of Se to be retained by tissues and to increase the activity of GSH−Px. When Se from bread and fish were compared (Meltzer et al., 1993), Se in bread was more effective than Se in fish for increasing serum and platelet Se concentrations. Alternatively, Se in beef (Shi and Spallholz, 1994) was more effective than sodium selenite, and only slightly less effective than SeMet, in restoring liver GSH−Px activity in the liver of Se-deficient rats. A study with Dutch men showed Se from bread and meat to be almost equally effective in increasing plasma, platelet, and erythrocyte Se concentrations (Van Der Torre et al., 1991).

The different results obtained with bread and meat sources of Se and Se in high-selenium garlic and broccoli can partially, although not totally, be explained by the known chemistry of these forms of Se. Most Se found in bread and meat is in the form of SeMet, and SeMet can effectively substitute for methionine (Butler et al., 1990). Thus, even if an individual is ingesting adequate Se on a daily basis, Se from bread and meat may continue to accumulate in tissues as a consequence of SeMet substituting for Met. Selenomethionine may also enter the pool available for selenoprotein production and excretion. First it is converted to selenocysteine (SeCys) by the trans-sulfuration pathway, and then a specific lyase releases the selenide (Vadhanavikit et al., 1993).

Assuming that the majority of Se in high-selenium broccoli and garlic is in the form of SeMC, then the initial metabolism of this Se would be to the methyl selenol (Vadhanavikit et al., 1993). The methyl selenol can then be metabolized by several pathways. Some could go into the pool that appears to be active against certain cancers (preliminary evidence from this laboratory now suggests that high-selenium broccoli decreases aberrant colon crypt foci in rats treated with 3,2′-dimethyl-4-aminobiphenyl). Another possible metabolic route is for the methyl selenol to be methylated and ultimately to be excreted in urine (Foster et al., 1986). Finally, it is possible that another specific lyase could convert the methyl selenol to selenide and thus allow the selenium to become incorporated into selenoproteins (Sunde, 1990). This accounts for the ability of Se from high-Se broccoli to replete GSH−Px activity, albeit rather inefficiently as compared to other sources of Se, in Se-deficient animals. One possibility that is not open to SeMC is replacement of methionine by SeMet because there is no way to form the SeMet in vivo.

Selenium from salts such as sodium selenite follow a pathway intermediate between SeMC and SeMet (Butler et al., 1990). Such Se can be more quickly converted to the hydrogen selenide pool than SeMet, but like SeMC, it cannot incorporate into SeMet and randomly substitute for methionine.

Many of the differences in absorption, retention, and excretion of Se between high-selenium garlic and broccoli and Se from meat, wheat, pure SeMet, and Se salts can be explained by assuming Se in the former group is predominately SeMC (Cai et al., 1995) that follows a metabolic pathway unique from Se in the latter group. However, there were still many differences between the studies that used Se from high-selenium garlic and studies that used high-selenium broccoli. These differences suggest that other factors also influence the metabolism. The differences in tissue retention of Se by rats fed high-selenium garlic at above the dietary requirement since weaning (Ip and Lisk, 1994) and rats from this study fed the dietary requirement after Se depletion shows that the Se status of the animal has a major effect. Differences between the present study and the human study (Finley et al., 1995) suggest that the concentration of Se in broccoli may have a major influence—perhaps by changing the chemical form of the Se. Further investigations are needed to clarify these questions before high-selenium broccoli can be recommended as a source of supplemental Se.

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