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Selenium metabolism in animals and humans

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Abstract——The main purpose of this paper is to point out the differences in the metabolism of Se between animals and humans. This is not to imply that the work with animals is not applicable to human because the use of animals in Se research has greatly assisted in understanding Se metabolism in human subjects. It is fair to conclude that until results are confirmed in humans it is risky to draw conclusions on Se metabolism in human based solely on animal data. Although animals have provided some extremely useful information on metabolism of Se, there is convincing evidence to indicate that some features of Se metabolism are unique to human. A few examples were given to support this contention.

Keywords: Se; metabolism; animals; human.

1 Major differences of Se metabolism

The majority of the Se in rat erythrocytes is associated with glutathione peroxidase (GPX) but in contrast the majority of Se is associated with hemoglobin in human erythrocytes (Whanger, 1986). There is only one Se gel filtration peak (sephadex G 150) in plasma from rats, but two are present in plasma from humans (Beilstein, 1983). Se deficiency alters the glutathione levels in plasma of rats (Hill, 1987) but has no influence on this compound in plasma from Se deficient humans (Xia, 1989). Se deficiency in humans causes a cardiac disorder called Keshan disease (Chen, 1980) but this does not occur in Se deficient rats. Cystathionase is present at high levels in hepatic tissues of fetal rats (Snell, 1973) but is absent in human fetal liver (Sturman, 1970). Dietary supplementation with selenomethionine (Semet) will increase the Se content of albumin in plasma of humans, but has no effect upon the Se content of albumin in plasma of rats (Whanger, 1994a). The molecular weight of selenoprotein W in human muscle is about three times that found in rat tissues (unpublished data from the author's laboratory).

2 Absorption

The absorption, transport, distribution, excretion, retention and metabolic transformation of Se is dependent on the chemical form and amount of the element ingested and on the presence or absence of numerous interacting dietary factors. Rats have been shown to absorb

92%, 91% and 81% respectively of trace doses of selenite, Semet and selenocystine, indicating almost complete absorption of these soluble selenium compounds. Studies with radioactive selenium at physiological levels indicate that the duodenum is the main site of Se absorption and that there is no absorption from the rumen or abomasum of sheep or the stomach of pigs or rats (Wright, 1966; Vendeland, 1992). There appears to be no homeostatic control of the absorption of selenite by rats because at least 95% was absorbed over a range of dietary Se intakes from deficient to mildly toxic levels. Total net absorption was about 85% of ingested Se in pigs but only 35% in sheep (Wright, 1966). This low intestinal Se absorption in ruminants is apparently related to a reduction of selenite to insoluble forms by rumen microorganisms(Ullrey, 1983; Ryssen, 1989).

Several studies conducted with humans have shown that the apparent absorption of dietary selenium ranges between 55% and 70%(Levander, 1986). Research conducted with New Zealand subjects demonstrated that the absorption of radioactive Semet by young women was much better than that of selenite (95% to 97% versus 44% to 70%). Subsequent work with stable isotope tracers confirmed the relatively poor absorbability by humans of Se as selenite as compared to other forms of this element(Christensen, 1983). The absorption of Se in eggs from chickens fed stable labeled Se was about 80% by pregnant and nonpregnant women. Similar to animals, humans appear to have very little homeostatic control over the absorption of Se. The apparent absorption was 57% and 70% before and after supplementation with high Se bread even though plasma levels rose almost three-fold during the intervention period(Combs, 1986).

3 Transport and distribution

Very early in the research on Se metabolism with humans in the author's laboratory it was realized that there was a difference between animal and human blood (Whanger, 1994b). The GPX activity per unit Se was significantly higher in animal blood than in higher primates even though all the blood samples contained 0.1 micrograms Se per ml blood. The GPX to Se ratio was very similar in blood from sheep, rats and squirrel monkeys, but in blood from rhesus monkeys and humans the ratio was only about 20% of that in animals. This suggested that the amount of Se associated with GPX was significantly less in higher primate blood than in blood from other animals.

This suspicion was confirmed by subjecting erythrocyte(RBC) lysates from humans and rats to gel filtration. The majority of the Se in rat lysate was found to be associated with GPX, but most of the Se in human blood lysates was associated with hemoglobin(Whanger, 1986). In further research to determine the reason for this difference, the effects of chemical forms of Se were investigated. When selenite was the form of Se in the diet for rats, most of the Se in the RBCs was found to be with GPX(Whanger, 1989). In contrast, most of the Se was with hemoglobin in blood of rats given Semet as the dietary form of Se. Since one of the major forms of Se in food consumed by humans is Semet(Whanger, 1994a) and selenite is

the most commonly used form of supplemental Se in diets for animals, this provided one reason for a difference between animals and humans.

The influence of chemical forms of Se was further studied with humans. Chinese and New Zealand residents were chosen for these studies because they are below the saturation plateau for GPX(Fig. 1). There is a significant correlation between blood Se levels and GPX activities in blood from residents of New Zealand and the Chinese living in the deficient areas, but there is not a correlation in blood of people living in the State of Oregon or South Dakota in the United States(Whanger, 1988). Even though Se is given to subjects in the United States and most other countries there is no further increase of GPX activity because they are already on the plateau for this enzyme. This is the reason that while blood Se levels are higher in residents of South Datota, USA, the GPX activity is similar to that of residents of Oregon, USA.

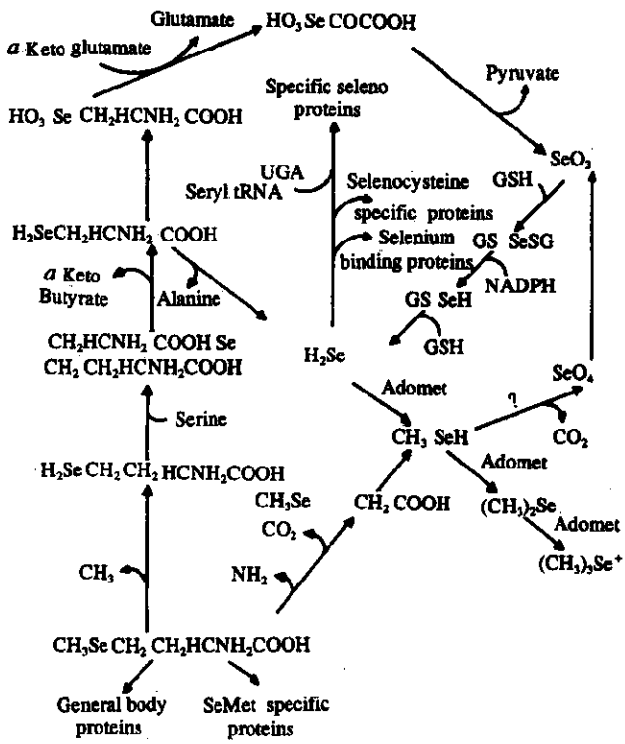

Fig. 1 Proposed metabolic pathways for selenium in animals and humans

The chemical forms of Se consumed may not be the only factor which needs to be considered in the metabolism of Se in humans. Differences were obtained in erythrocytes GPX activity in pregnant women in Oregon, USA, and pregnant women in New Zealand. A gradual increase of GPX activity was found in pregnant women living in Oregon as they approached parturition. A significant negative correlation ($r = -0.55$) was found between blood GPX activity and blood Se levels in oregon women(Butler, 1992) but a significant positive correlation ($r = -0.55$) was found between these components in New Zealand wom-

en. In contrast, a different trend was noted for pregnant women in New Zealand as they approached parturition. A gradual decline in GPX activiy was found in these women throughout pregnancy. The initial blood Se levels were about 0.18 ppm in the Oregon women which was in contrast to the level of 0.07 ppm for the New Zealand women. This differences in Se status was apparently responsible for this difference in GPX activity because all of the other factors were identical.

Se accumulated at a faster rate in New Zealand women taking Semet than in those taking selenate (Butler, 1991). The percentage of Se associated with GPX was significantly lower in both plasma and RBCs in women taking Semet than those taking selenate. Gel filtration of the plasma and RBC lystates revealed differences in the effects of the two forms of Se. Se was associated predominantly with hemoglobin in RBCs from women taking selenate. The Se content in RBCs of women taking selenate was not significantly different from the control group, but this content was significantly higher in RBCs from women taking Semet (Thomson, 1993). This is because the form of Se in hemoglobin is Semet and this selenoamino acid can not be synthesized from selenate by tissues. The tissues of study must be taken into consideration as well. For example, GPX activity was higher in platelets from women given Semet than the controls but this activity was even higher in platelets in blood from women who had taken selenate(Thomson, 1993). There were no differences, however, in GPX activity in plasma between women given selenate versus Semet.

Similar patterns were noted with Chinese men. Deficient Chinese men (Dechang) were given Se supplements as either selenate or Semet for one year. The Se accumulated at a faster rate in RBCs and plasma of men taking Semet than in those taking selenate, but there were no differences in the increase of GPX activity between these two groups of men(Xia, 1992a). The accumulation of Se in GPX in both RBCs and plasma was the same between the two treatment groups. However, this was not true for hemoglobin in the RBCs and the other proteins in the plasma. When Semet was given Se accumulated at a greater rate in hemoglobin in RBCs and other proteins in plasma than in these given selenate. The other proteins in plasma are albumin and selenoprotein P. The increase of Se in this fraction is primarily in albumin.

Even though there are two selenium containing proteins in RBCs, there are three major Se containing ones on the plasma (Whanger, 1994a). These are GPX, selenoprotein P and albumin and any of them could potentially serve as transport proteins. Se is presented in GPX and selenoprotein P as selenocysteine and as Semet in albumin(Deagen, 1991). Other workers have postulated that selenoprotein P plays a role in Se transport (Motsenbocker, 1982). The distribution of Se between these three Se containing proteins is dependent both upon the level of intake and the form of Se consumed. Differences were found in the gel filtration patterns of plasma from Chinese men living in Se deficient (Dechang), adequate (Shanghai) and excessive areas(Enshi) of China (Xia, 1992b). The gel filtration patterns of those men living in the excessive area(Enshi) was similar to that observed for rhesus monkeys given excess Semet (Butler, 1990). The majority of the Se in plasma from both sources

was associated with albumin. The pattern for plasma from the Chinese men is very similar to that for the monkeys, suggesting that the main dietary form of Se for the Chinese living in the Enshi area is Semet. This is consistent with the chemical analyses of the rice and corn grown in this area of China where Semet was the predominant form found (Beilstein, 1991).

Since gel filtration does not given complete separation of the Se containing proteins, a dual column procedure was developed to separate them in the plasma (Deagen, 1993). Except for residents in Enshi, China, the majority of the Se was associated with selenoprotein P from Chinese men living in deficient (Dechang), adequate (Shanghai) which is similar to that observed for rat plasma (Read, 1990). Supplementation with Semet for one year in subjects living in Dechang resulted in significant increases of this element with albumin. The large amount of Se with albumin in plasma from the men living in Enshi is consistent with the gel filtration patterns and suggests that Semet was the primary dietary form of Se consumed.

The dual column method was also used to study the distribution of Se between the three Se containing proteins in plasma from rhesus monkeys. Except when Semet was given, the majority of the Se was also associated with selkenoprotein P in monkey plasma (Deagen, 1993; Whanger, 1994b). The percentage of Se associated with albumin was significantly higher in those monkeys given elevated amounts of Semet. Interestingly, one month after removal of Semet from the diet, the percentage of Se associated with albumin was similar to that of the other groups.

The distribution of Se in the internal organs was studied with rats fed a commercial diet which contained about 0. 3ppm Se. The concentration of Se was highest in kidneys followed by liver, testes, adrenals, erythrocytes, spleen, pancreas, plasma, lungs, heart, thymus, muscle, and brain in declining order (Levander, 1986). A similar tissue distribution of Se was found in autopsy samples from Americans. It was highest in kindneys followed by liver, spleen, pancreas, testes, heart, muscle, lungs and brain in declining order. The total-body Se content of North Americans was calculated to be about 15 mg (range 13 to 20mg) whereas that of New Zealanders was estimated to be 3 to 6 mg (Levander, 1986). The content in the deficient Chinese was estimated to be around 1 to 1. 5 mg (Yang, 1989b). The Se status will have an influence on this pattern. When a tracer dose of selenite was given to rats fed a Se deficient diet, it concentrated in the testes, brain, thymus and spleens. The testes have a tenacious affinity for Se because this tissue lost the least amount of Se when rats were fed a Se deficient diet. In contrast to other tissues, Se accumulates at a very slow rate in the semen and reproductive organs of male animals.

In the search to find a suitable model animal for selenium metabolism in humans, the squirrel monkey was investigated first. Severe Se deficiencies were found to be produced in this animal after feeding a deficient diet containing vitamin E for 9 months (Muth, 1971). Much to our surprise the rhesus monkey was found to be much more resistant to Se deficiency since very few changes were observed after feeding a deficient diet with vitamin E for 4 years (Butler, 1988). In an effort to determine the basis for such a difference in response be-

tween these primates, the GPX activity with various hydroperoxide substrates and the glutathione transferase(GTF) activity were determine with liver samples from these two species of monkeys. The GPX activity with cumene hydroperoxide as the substrate and the GTF activity were found to be significantly higher in liver of rhesus monkeys as compared to squirrel monkeys (Whanger, 1989). GPX activity, however, was not different between these monkeys when either hydrogen peroxide or t-butyl hydroperoxide were used as substrates.

When the liver cytosols were subjected to gel filtration, 92% of the GPX activity with cumene hydroperoxide eluted with GTF activity in the rhesus monkey liver, but only 48% of this eluted with GTF in the liver of the squirrel monkey(Butler, 1988). This activity which eluted with GTF is sometimes called non-Se GPX and is due to the peroxidase properties of GTF (Prohaska, 1977). Since the total GPX activity with cumene hydroperoxide in rhesus monkeys was almost 4 times that for squirrel monkeys(Whanger, 1989), the percentage of activity does not give a true assessment of this difference. When the GPX cumene hydroperoxide activity (or non selenium GPX) was calculated, there was about 5. 5 fold greater amounts in the liver of the rhesus(92% times 865 units equals 796 units/mg protein) than in the squirrel (48% times 249 units equals 120 units/mg protein) monkeys (Whanger, 1989; 1993). Thus, this is proposed to be one of the reasons that the rhesus monkey is much more resistant to Se deficiency than the squirrel monkey.

The percentage of the non-Se GPX (or GTF) in livers of various species of animals has been determined. This percentage ranged from a low of 35 for rats to a high of 100 for the guinea pigs. Based on the high value for non-Se GPX for human liver, it would be predicted that it would also be difficult to produce Se deficiency in humans with adequate vitamin E status. Therefore, Keshan disease does not appear to be a pure Se deficiency but other factors may also be involved. In support of this it was impossible to produce Se deficiency lesions in rhesus monkeys unless they were also made protein deficient (Butler, 1988). Another reason to suspect other factors are involved is that children with inborn error of metabolism such as maple syrup disease and phenylketonuria have just as low blood and hair Se levels, and GPX activities(Lombeck, 1987), but they do not develop cardiovascular disorders like Keshan patients. Some recent Chinese work indicate factors other than Se deficiency as the sole causative factor of Keshan disease(Yang, 1994). When rats and guinea pigs were fed a Se deficient purified diet no obvious changes were seen in ultrastructure and oxidative phosphorylation of mitochondria, but when fed cereals from Keshan disease endemic areas there were significant abnormalities. However, when the diet from the Keshan disease area was supplemented with Se all the abnormalities were reduced significantly. Based on the rules with the purified diet, it was concluded that Se deficiency alone can not induce severe heart damage in experimental animals.

Dr. Janghorbani's group was the first to use the stable isotope tracer approach for studies of Se metabolism(Janghorbani, 1981). This method has since been used by them and other investigators since that time to address a number of metabolic issues in humans (Janghorbani, 1987). They have applied this approach to the question of measurement of Se pool

sizes directly in humans subjects (Martin, 1988; 1989) and formulated the concept of selenite exchangeable metabolic pool (Se-EMP) specifically for the purpose of assessment of Se status in humans over a wide range of chronic Se intake. This group has conducted a number of studies in humans and animals (Janghorbani, 1990a; 1990b; 1991) to explore the quantitative relationship between the size of Se-EMP and various accepted indices of Se status. Experiments have been conducted on the reproducibility of the measurements, the quantitative relationship between the size of Se-EMP (^{w}Se-EMP) and whole body Se content, and the sensitivity of ^{w}Se-EMP to alterations in Se status.

Se depletion experiments in rats have been conducted to examine the sensitivity of ^{w}Se-EMP to change in whole body Se content by monitoring timed measurement of carcass Se, liver Se, and liver GPX. The carcass and liver Se content were found to be respectively 53% and 16% of the total body Se. The 7-day average values, which is called a test module, for ^{w}Se-EMP for control and Se-restricted rats were 8.5 plus or minus 0.20 and 4.5 plus or minus 0.23 micrograms, respectively (Martin, 1989). Several independent experiments have shown excellent linear quantitative correlations between ^{w}Se-EMP and whole body endogenous Se in rats and this was independent of the chemical form of Se, the previous Se intake, or the size or age of the animal (Janghorbani, 1990a, 1991). Similar data are presently being collected with Chinese subjects with various Se status to obtain additional information on Se metabolism in humans. As noted earlier, the Chinese populations with such varied Se status are ideal groups for this purpose.

A number of studies have been conducted to establish the feasibility of the concept of Se-EMP in humans subjects (Matin, 1988, 1989). Based on these experimental data and present knowledge of the biochemical pathways for metabolism of Se, the concept of Se-EMP as a potential by useful approach to assessment of Se status in human subjects was proposed (Janghorbani, 1990b). The route of administration was shown to have no effect upon the Se-EMP in humans (Janghorbani, 1990b), and thus the label can be given intravenously which eliminates the collection of feces. These studies showed that the following important points: (1) ^{w}Se-EMP comprises a major fraction of total body Se (Janghorbani, 1987); (2) the magnitude of Se-EMP is numerically the same whether the selenite label is administered restriction (Martin, 1989); and (3) the size of Se-EMP responds to dietary Se-restriction (Martin, 1989; and (4) ^{w}Se-EMP indicates a potentially important effect of such variables as ascorbic acid status on Se pool sizes.

With the development of inductively coupled plasma mass spectrometry (Janghorbani, 1990b), a more precise and accurate method of isotopic analysis became available compared with the previous method of neutron activation analysis. This new technique permitted a focus on the issues of accuracy and repeatability of ^{w}Se-EMP in humans. This was demonstrated with some experiments with home total parenteral nutrition patients in the United States. While on Se-restricted formulas, the ^{w}Se-EMP ranged from 500 to 900 micrograms when adults were on home total parenteral nutrition without Se in their formulas. When the subjects were given Se supplementation of selenite (60 micrograms Se per day) for three months

the ^{77}Se-EMP pool increased to 6000 micrograms. The data demonstrated that all normal induces of Se status indicated extremely low body Se prior to institution of Se supplement; ^{77}Se-EMP reflected this low Se status; and after three months of Se supplementation plasma Se and plasma GPX activity reached normal level. This normalization was clearly reflected in a large increase of ^{77}Se-EMP. Experiments with Chinese subjects with wide Se status are presently in progress to confirm the American data.

The use of stable isotopes of selenium have been used by others to investigate selenium metabolism in humans. A kinetic model for the metabolism of selenite in humans was developed (Patterson, 1992). This model was rejected because it did not simulate the metabolism of Se with normal Se in humans. The main reason for this is because the main source of Se intake is the organic form. A kinetic model using stable isotopes of Semet appeared to be more appropriate (Swanson, 1991). The model included absorption and distribution along the gastrointestinal tract, uptake by the liver-pancreas subsystem, enterohepatic recirculation, distribution to two large tissue pools, and transport through four components of the plasma pool.

4 Excretion of selenium

Urinary excretion of Se has been studied as a possible indicator of Se status. Urinary Se levels have been reported to range from a low of 7 nanograms per ml in the deficient areas of China to 2680 nanograms per ml for people living in the toxic areas of that country (Yang, 1983). Although urinary trimethyl selenium (TMSe) was once thought to be a detoxification product of Se, its levels in the urine are seldom above 5% of total unless it is injected. Data obtained with rat studies have indicated that TMSe constitutes a major fraction of the urine Se when high levels were either provided in drinking water or were injected, but under oral intake conditions relevant to human circumstances it is usually a minor component of the total urine Se (Nahapetian, 1984). This has been confirmed in studies with men living in the high Se areas of China. Even though the Se intake was as much as 700 micrograms per day, the TMSe content in the urine never exceeded 7% of the total excreted (Xia, 1992b). The excretion of Se in urine was (in micrograms per day) $3.4+1.1$, $24.4+12$ and $650+384$ for men living in Dechang, Shanghai and Enshi, respectively. The TMSe with respect to total Se excreted increased from nondetactable in Dechang men to 2% in men from Shanghai and 7% of total Se in those living in Enshi. A linear response was obtained with renal clearance with the Se status of the subjects. The regression of renal clearance with plasma Se was calculated to be 0.83 which is statistically higher significant. The chemical forms of Se will also affect the renal clearance. It took a higher total plasma Se content in men consuming Semet to result in the same renal clearance of Se as in those consuming selenate (Xia, 1992a). There was no overlap of any of the values for men consuming Semet in camparison with those consuming selenate. Se content in GPX and Se in the other proteins were also plotted against renal clearance, but neither of these were as significant as clearance for total plasma Se.

The pulmonary excretion of volatile Se compounds in rats is significant only when subacute doses of soluble Se salts are injected. Negligible losses of Se via the pulmonary or dermal routes were observed when human took microgram oral doses of selenite or Semet, and no pulmonary excretion was detected in a subject given one mg Se as selenite (Levander, 1986).

Use of radioactive selenite with rats indicated the existence of threshold levels of dietary Se when given as selenite (0.054—0.084 micrograms/g) above which urinary Se excretion is directly related to its dietary level. However, below this level there was not such a relationship. In humans, the amount of Se excreted in the urine is closely related to the dietary intake, and balance studies have shown that over a range of intakes from 9 to 226 micrograms per day the urine accounts for 50% to 60% of the total amount excreted (Combs, 1986). Elimination of urinary Se excretion below the dietary threshold is an important mechanism for Se conservation during periods of low Se intake (Burk, 1973). This was demonstrated by work in New Zealand which indicated that people of low Se status had low renal plasma clearances of this element (Robinson, 1985).

Fecal excretion of Se is greater in ruminants than in monograstic animals. When sheep and swine were given oral doses of radioselenite, they excreted 66% and 15% respectively of the dose via this route (Wright, 1966). The rumen microorganisms are responsible for this difference because they reduce selenite to unavailable forms (van Ryssen, 1989). Less Se is reduced to these unavailable forms when it is in organic forms. Thus, the increase fecal excretion in ruminants is due to poor absorption rather than elevated endogenous excretion. Chinese men residing in a Keshan disease area and consuming about 9 micrograms daily in the diet excreted about 3.4 micrograms per day or about 38% of their total excretory output in their feces, whereas young North American males adjusted to a dietary Se intake of 226 microgram per day excreted 86 micrograms or 43% of their total excretory output in their feces (Lavander, 1986). These studies show that fecal excretion accounts for a relatively constant fraction of the total excretory output over a wide range of dietary intakes.

Yeast Se shown to be more effective than selenite in increasing the Se content in maternal serum and milk, and in infant serum (Kumpulainen, 1985). The data suggest that maternal daily intake of 50 to 75 micrograms is adequate during lactation. Stable isotopes studies with lactating women indicated that milk contained more Se from Semet than that from selenite (Mangels, 1990). Similar information was obtained in rat studies. Semet, Se yeast and selenite were fed in diets at 3 different levels (0.1, 0.25, and 0.5 ppm) to lactating rats and based on scope ratio analyses the bioavailability of Semet and Se yeast was greater than that of selenite in both lactating dams and their nursing pups (Smith, 1987). The greater availability of organic Se to pup tissues was suggested to be the direct result of the greater content of Se in milk of dams. Most of the Se in human milk is protein bound (Milner, 1987). At least nine selenium containing proteins were detected in human milk and GPX accounted for 15% to 30% of the selenium in milk. There is a difference in the distribution of selenium in various milk components between humans and animals (Debski, 1987; van Dael,

1987). From 8 to 12 selenium containing proteins were also found in cow and goat milk. Percent of total peroxidase activity associated with GPX was 29, 27 and 65 respectively for human, cow and goat milk(Debski, 1987). Se in the whey fraction accounted respectively for 72%, 62% and 30% of the total in cow, human and goat milk. Slightly different results were obtained by other investigators who examined milk from human, cows, goats and sheep (van Dael, 1994). More Se was associated with whey in human milk than this fraction from cow, goat and sheep milk. The case in fraction from sheep milk contained more Se than this fraction from any of the other animals.

5 Retention of Se

The whole body retention of a single dose of radioselenite injected into rats consists of two or more components(Burk, 1973). Since each tissue within the body has its own discrete rate of Se turnover, the apparent whole-body retention of radioselenium is the summation of several different processes. The biological half-lives of radioselenium in rat skeletal muscle, whole body, and kidneys were respectively 74,55 and 38 days. The whole-body turnover of Se in humans can also be expressed by a three-term exponential curve(Griffiths, 1976). The oral dose of radiolabelled Semet during the third phase was 234 in New Zealanders of low Se status whereas that for selenite was only 103 days. This is in agreement with the finding that Semet is more effective than selenite in raising blood Se in persons of low Se status (Butler, 1989; Xia, 1992a). Stable Se isotopes given as selenite was used to estimate whole-body Se retention in North Americans, and the half-life calculated for the longest exponential component was 162 days(Janghorbani, 1987). The shorter half-life for the New Zealanders may be because they are below the Se saturation plateau in contrast to North Americans.

The chemical forms of Se has an influence on its retention. Much greater retention was found with Semet than with selenite in rats(Beilstein, 1988). There was 30% retention with Semet as compared to much lower amounts of 14% with selenite. Similar differences in retention were found with high Se wheat versus selenite in sheep(van Ryssen, 1989). Since the major form of Se in wheat is Semet(Beilstain, 1986), this difference is postulated to be due to this form of Se. Se as selenocysteine is metabolized more like selenite than like Semet (Deagen, 1987), and thus all organic selenocompounds are not metabolized alike. Probably one reason for this is that selenocystaine lyase converts selenocysteine to alanine plus selenide(Esaki, 1982), and the selenide enters the same metabolic pool as that from selenite. Se status had no effect upon the activity of selenocysteine lyase(Deagen, 1987) and thus it is not influenced by Se intake. The activity of this enzyme, however, is influenced by the vitamin B_6 status. Both animal and human studies indicate an inverse relationship between Se status and retention(Ullrey, 1983; Xia, 1992b).

Consistent with animal studies, Se as Semet was much more effective in increasing blood selenium levels than selenate(Thomson, 1993; Xia, 1992a). This is presumed a reflection of increased retention. Supplementation with Se enriched wheat or yeast was shown to raise

blood levels in Finnish men with low initial levels more effectively than with selenate (Levander, 1986). Furthermore, once the supplements were discontinued, the subjects given the wheat or yeast had higher blood levels several weeks later than the group given selenate. This is probably due to the presence of Se in wheat and yeast as Semet (Beilstein, 1986).

6 Metabolic transformation of Se

Fig. 1 gives proposed pathways for the metabolism of Se in animals and humans. Many of these reaction were derived with studies on sulfur metabolism, and is assumed to be similar for Se. However, it should be noted that there is one very obvious difference in the metabolism of Se and that is in general sulfur compounds tend to undergo oxidative pathways whereas Se compounds tend to follow reductive pathways (Ganther, 1965). Selenate appears to be generated by either the reduction of selenite to this compound or the conversion of Semet to it (Wang, 1992). The mechanism of how selenate is reduced to selenite in animals is not known, but is assumed to involved ATP sulfurate. The route for reduction of selenite to selenide is the most clearly understood metabolic pathway for Se (Ganther, 1971). Selenite reacts spontaneously with sulfhydryl compounds such as GSH to form glutathione selenotrisulfide or sometimes called selenodiglutathione. Glutathione reductase acts on this selenocompound to form selenopersulfide, which is then reduced in the presence of GSH to selenide. At this level there are number of options available for selenide. It can be acted upon by thiol methyltransferase to form methylselenol and subsequently to dimethylselenide (Hsieh, 1977). The dimethylselenide is acted upon by thioether methyltransferase to produce thrimethyl selenide (Foster, 1986). S-adenosylmethionine (Adomet) is a necessary cofactor for all there of these reactions. These methylated compounds of selenium are regarded as detoxified forms of this element.

The presumed major catabolic pathways for Semet are either transsulfuration or transamination-decarboxylation. The transsulfuration pathway allows the synthesis of selenocysteine using serine. The two enzymes responsible for synthesis (cystathionine synthetase) and cleavage (cystathionine lyase) of selenocystathione require pyridoxal phosphate for activity. Although Semet has not been definitely shown to be converted to selenocysteine by this pathway, the seleno analogues for cystathionine synthase and lyase are efficient substrates for them (Esaki, 1981). Thus it is reasonable to assume that Semet can be catabolized by this pathway. However, some work with blood from human patients with deficiencies of three of the enzymes of the transsulfuration pathway do not fully support this possibility (Beilstain, 1989). Utilization of Semet for GPX synthesis was not impaired by erythrocytes from these subjects. The selenocysteine generated from the cleavage of selenocystathione can then be acted on by selenocystasine lyase to produce alanine and selenite (Esaki, 1982).

The other pathway for catabolism of Semet is the transamination-decarboxylation route.

Through transamination and decarboxylation this compound can be converted to form 3-methylselenopropionic acid. This conversion requires two enzymes which also depend upon pyridoxal phosphate for activity. This compound through a series of reactions can be converted to methylselenol (Steel, 1978; 1979). It is estimated that about 90% of dietary methionine, and presumably Semet, is metabolized through this pathway. Although the conversion of this compound to selenate appears rather remote, it should be noted that evidence for selenate in urine of rats has been presented (Beilstein, 1989).

In addition to catabolism Semet can be incorporated either into general proteins or into Semet specific proteins. The sulfur status of the animal is one of the major factors affecting the catabolism of Semet(Butler, 1989). With high sulfur intake as methionine more Semet is diverted to the catabolic pathways and the conversion of it to selenocysteine is increased. Presumably selenocysteine could also be converted to selenocysteine seleninic acid. This compound with alpha glutamate could be converted to β-seleninyl pyruvate which is then converted to selenite.

As just noted the metabolism of Se leads to several possible precursor forms of Se that can be used for the synthesis of selenoproteins. Sunde has divide selenoproteins into four different classes depending on the Se precursors and the mechanism used for Se incorporation (Sunde, 1990). One class is the methionine-specific proteins which have Semet as the Se moiety and is incorporated translationaly into a growing peptide chain at positions specified by the methionine codon. The Se stoichiometry will depend on the ratio of Semet versus methionine esterified to $tRNA^{met}$. Specific examples include thiolase, β-galactosidase and possibly the muscle in Semet-fed animals. A similar class of selenoproteins is the selenocysteine-specific proteins which have preformed selenocysteine as the Se moiety and is incorporated translationally at positions specified by cystine codons using cystine $tRNA^{cys}$. Some examples of this class would include the competitive incorporation of selenocysteine and cysteine into protein in a cell-free translation the competitive incorporation of selenocysteine and cysteine into protein in a cell-free translation system using globin mRNA and the apparent selenocysteine-specific proteins in yeast. The most important class of selenoproteins is the Se spesific ones. The discovery that UGA codes for the selenocysteine in these selenoproteins is the unique characteristic of this group of proteins. Such selenoproteins as GPX, deiondinase, selenoprotein P, mitochondria capsule slenoprotein, selenoproteins W and the bacterial ones like formate dehydrogenase, glycine reductase and hydrogenase fall in this class. Selenocysteine is the Se moiety but the Se is incorporated cotranslationally using selenide and serine as the precursors in $tRNA^{seruga}$-mediated process at the position specified by a UGA codon. The fourth class of selenoproteins is the Se-binding ones. This operational class contains the selenoproteins with Se bound tightly enough so that the Se remains attached during standard protein purification procedures that produce discrete ^{75}Se-labeled species. These include the fatty acid binding protein, the 130-kD plasma Se binding protein and the 77-kD mitochondrial Se binding protein in animals and possibly the bacterial xanthine dehydrogenase. The reduction of selenite to selenide, the methylation of this reduced compound and the incorpora-

tion of Se from either selenide or Semet into proteins have been shown to occur with these selenocompounds in animals. The presence of TMSe in urine and dimethylselenide in breath, and the increase of GPX activity with selenate or Semet supplement suggest that some of these reactions also occur in humans. The other reactions in Fig. 1 have not been shown to occur for the selenocompounds but are presumed to take place because of the demonstration with the sulfur compounds.

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