Selenomethionine: A Review of Its Nutritional Significance, Metabolism and Toxicity

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ABSTRACT Although the need for selenium in human and animal nutrition is well recognized, the question concerning the proper form of selenium for supplemental use is still being debated. Ideally, selenium should be supplemented in the form in which it occurs naturally in foods. Because the L-isomer of selenomethionine (Se-met) is a major natural food-form of selenium, synthetic L-Se-met or enriched food sources thereof such as selenium yeast are appropriate supplemental forms of Se for humans; for animals, DL-Se-met is acceptable. Ingested Se-met is either metabolized directly to reactive forms of selenium or stored in place of methionine in body proteins. Se-met metabolism is closely linked to protein turnover. At constant intakes in the nutritional range, tissue Se levels increase until a steady state is established, preventing the build-up to toxic levels. J. Nutr. 130: 1653–1656, 2000.

KEY WORDS: • selenium • selenomethionine • selenium yeast • selenoproteins • selenium metabolism • toxicity

Selenomethionine (Se-met) along with other seleno amino acids was suspected already in the mid 1930s to be one of the toxic components of seleniferous plants (1), but suggestive experimental evidence for its presence in seleniferous wheat protein hydrolysates was obtained only in 1949 (2). Se-met was definitely identified in plant proteins in the 1950s–1960s and was concurrently also shown to be produced by strains of Saccharomyces cerevisiae, Candida albicans, Escherichia coli, rumen bacteria and marine algae, when these were grown in Se-containing media. (3) In 1962, 75Se-met became available and was introduced as a pancreatic radioimaging agent (4). In the mid-1970s, metabolic studies indicated that Se-met is well absorbed and retained, suggesting its use for nutritional Se supplementation (5). At about the same time, high Se-yeast was introduced as an economical food source of Se-met. By 1984, synthetic L-Se-met was also beginning to be produced at a cost comparable to that of Se-yeast on a per-Se basis. Numerous experimental studies have since established that Se-met and Se-yeast are suitable for nutritional Se-supplementation (6–8). However, concerns have also been raised that Se-met might, under some conditions, accumulate in, or be released from body stores to toxic levels (9,10). This review addresses these concerns within a more general description of its occurrence, metabolism and toxicity.

Biosynthesis. Cereals and forage crops convert Se mainly into Se-met and incorporate it into protein in place of methionine (Met) because tRNA\textsuperscript{Met} does not discriminate between Met and Se-met. The major pathway of Se-met synthesis by plants, marine algae and yeast is shown in Figure 1. Se-met is not required for growth by plants but is produced along with Met in quantities depending on the amount of Se available. In plant tissue of the grassland legume species Melilotus indica, for example (11), Se-met contents increased with increasing soil Se concentrations until Se-met accounted for >50% of the total Se content of the plant. In contrast, selenocysteine (Se-cys) methyl-Se-cys and γ-glutamyl-Se-methyl-cys remained at relatively low levels irrespective of soil Se content and were not significantly incorporated into plant protein. In seleniferous corn, wheat and soybeans, Se-met contents ranged from 81 to 82% of total Se (12). S. cerevisiae may assimilate up to ∼3000 μg/g Se (13). Such yeasts contain 90% of the total Se in the form of L-Se-met (8,14) and only traces of inorganic Se; additional organoselenium compounds detected, in percentage of total Se, include Se-cys (0.5%), selenocystathionine (0.5%), methylselenocysteine (0.5%), γ-glutamyl-Se-methylselenocysteine (0.5%) and 2–5% Se-adenosylselenohomocysteine (Uden, P., ICP-MS results on samples provided by author, 1999). Se-met is synthesized analogously to Met as evidenced from the fact that a mutant strain of yeast unable to synthesize Met also failed to produce Se-met, when grown in Se-containing media (15). It should be noted that some Se yeasts that contain Se predominantly as selenite or selenate are marketed; the need to distinguish between these two types has been emphasized (16).

Selenomethionine-Containing Proteins and Enzymes. The replacement of Met by Se-met as a rule does not significantly alter protein structure but may influence the activity of enzymes if Se-met replaces Met in the vicinity of the active site. Because the CH\textsubscript{3}-Se group of Se-met is more hydrophobic than the CH\textsubscript{3}-S-moiety of Met, substrate access may be affected, altering the kinetic parameters. The Se-met–substituted thymidylate synthase of E. coli, for example, exhibited a 40% higher specific activity than the normal enzyme (17). Similarly, the K\textsubscript{m} of the Se-met–substituted phosphomannose isomerase from C. albicans, which normally contains four Met residues in the vicinity of the active site, was fourfold higher as well as the inhibition constant for zinc ion (18). In β-galactosidase of E. coli, replacement of more than half of the 150 Met residues by Se-met resulted in inactivity of this enzyme (19). Compared with the normal enzyme, the thermal stability of Se-met–substituted thymidylate synthase of E. coli was lowered eightfold and its sensitivity to dissolved oxygen was significantly enhanced (17). Because Se-met oxide is easily reduced back to Se-met by glutathione (GSH) (20), oxidative damage to Se-met is reversible. On the basis of this observation, Se-met and GSH were suggested to act as an antioxidant system, protecting cells against oxidants such as peroxynitrite. However, it is still not certain whether this occurs in vivo; a recent study failed to show such a protective effect with human plasma proteins (21). Se-met also has radioprotective
properties (22) and protects against UV-light–induced skin damage in mice (23).

Selenomethionine in Organs and Tissues. Because higher animals have no efficient mechanism for Met synthesis, they are also unable to synthesize Se-met. Accordingly, only Se-cys, and no Se-met, was detected in rats supplemented with Se as selenite (24). The question thus arises whether Se-met has specific essential or beneficial functions in the organism. Although selenite or selenate may be used for selenoprotein biosynthesis, only Se-met is incorporated into body proteins (25). This allows Se to be stored in the organism and reversibly released by normal metabolic processes, thus offering an advantage over other Se compounds, along with other possible beneficial effects mentioned above. Ingested Se-met is absorbed in the small intestine via the Na$^{+}$-dependent neutral amino acid transport system (25). Any Se-met that is not immediately metabolized is incorporated into organs with high rates of protein synthesis such as the skeletal muscles, erythrocytes, pancreas, liver, kidney, stomach and the gastrointestinal mucosa; the retention was similar to that observed with $^{35}$S-methionine and $^{14}$C-phenylalanine (26). In rats fed a basal Se-deficient diet with 2 mg/g Se added as Se-met, the level of Se in muscle was 10 times that of rats fed the equivalent amount of selenite or selenate (27). The Se contents of human skeletal muscle reflect accordingly the dietary Se-met intakes and were found to be the highest in Japanese adults (1700 ng/g), followed by Canadians (370 ng/g) and Americans (240 ng/g), with the lowest (61 ng/g) found in New Zealand adults (28). Erythrocytes incorporate Se-met mainly into hemoglobin (9). In plasma, it is found primarily in the albumin fraction; in Chinese men of low Se-status, the albumin fraction contained 20% of the total Se, but reached 47 ± 5% in men residing in a high-Se region (29). Se-met was also detected in human milk (35). In nursing mothers, Se-met or Se yeast prevented the decline of plasma Se and glutathione peroxidase (GSH-Px) activity as well as the decline of Se in milk; significantly more Se appeared in milk of mothers consuming Se-met than selenite (36,37).

**Metabolism and Availability for GSH-Px Synthesis.** Se-met is activated initially by adenosylation, demethylated and converted to Se-cys via selenohomocysteine and selenocystathionine in analogy to Met and without involving Se-met–specific enzymes (38). The Se-cys formed is degraded further in the liver to serine and selenide; the latter is either used for selenoprotein synthesis or methylated to dimethyl selenide and trimethylselenonium ion and exhaled or excreted. Evidence for degradation of Se-met to methylselenol (CH$_3$SeH) by γ-lyase action has also been obtained (39), see Figure 2. The rate of degradation of Se-met is rapid, as evidenced from the similar rates of appearance and disappearance of inorganic Se metabolites in rat serum after oral administration of Se-met or selenite (33). Se-met metabolism is dependent on vitamin B-6 status, because B-6–dependent enzymes are involved in the metabolic activation of Se-met (40). Tissue deposition of Se-met and its utilization for GSH-Px synthesis also depend on Met status. In Met-deficient rats supplemented with Se-met, GSH-Px activity was lower than in Se-met supplemented, Met-adequate rats (41). In another study (42), dietary Met and the percentage of Se associated with GSH-Px were correlated directly. Similarly, supplemental Met increased RBC GSH-Px activity in adult Chinese men with low Se status with limiting dietary Met intakes (43). In Met-adequate subjects, supplemental Se-met causes tissue Se levels to increase in proportion to dosage until a steady state is reached. Erythrocyte Se, for example, begins to plateau after 6 wk of supplementation (43).
Toxicity. The median lethal dose (LD₅₀) of Se-met in rats given an intraperitoneal injection was determined to be 4.25 mg Se/kg body (44) and thus is comparable to that of selenite or selenolate. In mice, the LD₅₀ of DL-Se-met was 8.8 ± 1.37 mg Se/kg, and the minimal lethal dose, 4.0 mg Se/kg, after intravenous injection (45). The chronic toxicity of Se-met is lower than that of selenite (46). In a 30-d trial with long-tailed pregnant female Macaques (Macaca fascicularis) (47), the highest tolerated dose of L-Se-met was estimated at 150 μg Se/(kg·d). Erythrocyte Se, plasma Se and hair Se associated with increased weight loss due to Se toxicity were >2.3 mg/L, >2.8 mg/L and >27 μg/g, respectively, and were consistent with the cut-off values for humans subsisting on a predominantly vegetarian diet, as determined in a Chinese study (48). Both the L- and D-Se-met isomers exhibited the same toxicities in rats and both isomers were retained in skeletal muscle, heart, liver and the erythrocytes to a similar degree; only the plasma Se levels were lower in the rats receiving L-Se-met (49). However, in mallard ducklings, L-Se-met was significantly more toxic than DL-Se-met (50,51). In cultured murine and human lymphoid cells, DL-Se-met was only half as cytotoxic as the L- and D-Se-met, and only L-Se-met was a good substrate for adenosylmethionine synthase (39). Human lymphoblast cells from subjects with transsulfuration defects metabolized DL-Se-met poorly, although these cells utilized selenoprotein P (52). The differential responses of normal cells to L- and D-Se-met thus are attributable primarily to the initial steps of Se-met metabolism involving stereospecific transsulfuration enzymes. Because of these effects, it would appear preferable that L-Se-met rather than DL-Se-met be employed for human Se supplementation, although for animals, the DL-mixture would be acceptable. The concern (9,10) that the incorporation of Se-met into body proteins could increase Se to toxic levels is not warranted because a steady state is established, which prevents the uncontrolled accumulation of Se. Similarly, the release of Se-met from body proteins by catabolic processes during an illness should not result in Se toxicity because no mechanism for the selective release of Se-met during catabolism exists.

Nutritional Dosage and Safety. Dietary Se intakes depend on regional Se availability and the types of foods consumed. In American adults, Se intakes typically range from 80 to 165 μg/d (53). Although observations of subjects residing in high Se regions or taking Se supplements previously identified Se intakes of up to 724 μg/d by adults as safe, it is considered approximate. To provide a sufficiently wide margin of safety, the reference dose (RfD) for Se from all nutritional sources for a 70-kg human has been set at 350 μg/d (10), corresponding to 5 μg Se/(kg body · d) or 5 times the recommended dietary allowance. The RfD thus defines as safe the total intake of Se by an American adult who is subsisting on a normal diet and is taking an additional 200 μg Se/d in the form of a nutritional supplement. The RfD may still be revised pending the outcome of ongoing studies by the Environmental Protection Agency, but is unlikely to change significantly in the light of currently available evidence.

Summary and Perspectives for the Future. Because Se-met cannot be synthesized by higher animals and humans, it could have beneficial physiologic effects not shared by other selenium compounds. Future studies should focus on identifying such effects and may uncover specific therapeutic roles of Se-met. This applies especially to organs with a high affinity for Se-met such as the skeletal muscles, the pancreas, the brain and the cells of the immune system. Such studies will further justify the use of Se-met in human and animal nutrition and its applications in the prevention of cancer and other diseases.

LITERATURE CITED
