GLOBAL IMPORTANCE OF SELENIUM AND ITS RELATION TO HUMAN HEALTH

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Keywords: Selenium, selenide, methylselenol, selenite, selenocysteine, selenomethionine, methylselenocysteine, cardiomyopathy, Keshan Disease, Kaschin-Beck Disease, cancer, chemoprevention, selenoenzymes, immune system, apoptosis, carcinogenesis

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Summary

Selenium is an essential biological trace element. It is an essential constituent of several enzymes in which it is present in the form of the unusual amino acid selenocysteine (SeCys). Selenium intakes of at least 40 mcg per day appear to be required to support

the maximal expression of the SeCys enzymes; this level is greater than the typical intakes of many people in several parts of the world. Selenium deficiency is associated with sub-optimal expression of one or more of the Se-enzymes, resulting in impaired antioxidant protection, redox regulation and energy production. These effects appear to contribute to health problems caused by environmental oxidative stresses and infections. Selenium intakes greater than those required for maximal SeCys-enzyme expression appear to reduce cancer risk. Present evidence suggests that this protection occurs by supporting the expression of the SeCys-enzymes with antioxidant and redox-regulatory functions, as well as by serving as a source of anti-tumorigenic Se-metabolites. Accordingly, increasing Se intakes can be expected to reduce morbidity and mortality in many parts of the world.

1. Introduction

Selenium (Se) was first recognized as an essential nutrient in the late 1950s when it was found to replace vitamin E in the diets of rats and chicks for the prevention of vascular, muscular and/or hepatic lesions. Until that time, Se had been thought of only as a toxicant, being associated with "alkali disease" in grazing livestock in the northern Great Plains of the United States. Since that time, Se has become the subject of investigations in many parts of the world (see *Agronomic Approaches to Increase Selenium Concentration in Livestock Feed and Food Crops*). From this work has emerged the current view of Se as an essential trace element important in human health, both for averting morbidity associated with deficiency as well as reducing cancer risks at supranutritional intakes.

2. Metabolic Roles of Selenium

In the early 1970s, Se was found to be an essential component of the enzyme glutathione peroxidase (GPX). As that enzyme was known to participate in the antioxidant protection of cells by reducing hydroperoxides, this finding was taken to explain the nutritional "sparing" by Se of vitamin E, a known lipid-soluble antioxidant. Discoveries over the last 15 years have revealed that several Se-enzymes are recognized (Table 1): at least five GPX isoforms, three iodothyronine 5'-deiodinases (DIs), three thioredoxin reductases (TRs), and selenophosphate synthetase. Other proteins are recognized as specifically incorporating Se, although their metabolic functions remain unclear: plasma selenoprotein P, muscle selenoprotein W, and selenoproteins in prostate and placenta. Each of these contains Se as the amino acid selenocysteine (SeCys). Selenium is incorporated into SeCys by the co-translational modification of tRNA-bound serinyl residues at certain loci encoded by specific TGA codons containing SeCys-insertion sequences in the 3'-untranslated regions of their respective mRNAs. Thus, TGA is decoded as SeCys rather than as a stop signal. It is likely that more SeCys-proteins remain to be discovered, as other Se-containing proteins have been identified.

Protein	Subunit Mass KDa	SeCys content moles/mole	Enzymatic function	Tissue distribution
GPX-1	22	4	GSH-dependent	cytosol and

		(tetramer)	reduction of H_2O_2 or lipoperoxides	mito-chondrial matrix space; ubiquitous
GPX-2	22	4 (tetramer)	GSH-dependent reduction of H_2O_2 or lipoperoxides	Gastrointestinal tract
GPX-3	23[a]	4 (tetramer)	GSH-dependent reduction of H_2O_2 or lipoperoxides	Plasma
GPX-4	19	1	Phospholipid hydroperoxide removal	Ubiquitous
DI-1	28	1	conversion of T_4 to T_3	thyroid, liver, kidney, brain, pituitary
DI-2	30.5	1	conversion of T_4 to T_3	pituitary, thyroid, heart, muscles
DI-3	31.5	1	conversion of T_4 to rT_3	Placenta, brain, skin
TR-1	55	2 (dimer)	NAPDH-dependent reduction of oxidized thioredoxin	cytosol; ubiquitous
TR-2	53	2 (dimer)	NAPDH-dependent reduction of oxidized thioredoxin	Mitochondria; kidney, liver, adrenal, heart
TR-3	57	2 (dimer)	NAPDH-dependent reduction of oxidized thioredoxin	Ubiquitous
Selenophosphate synthetase	48	1	ATP-dependent formation of selenophosphate from selenide	liver, testes, kidney thymus, spleen
SeP	57[a] (43 net)	Up to 10 (monomer)	Unknown	Plasma
SeW	10	1	Unknown	Muscle
Prostate Se-protein	15	1	Unknown	Prostate
Placental Se-protein	15	1	Unknown	Placenta

[a]glycosylated

Table 1. The known SeCys-proteins.

The dietary requirements of animals for supporting the expression of SeCys-enzymes are generally satisfied by dietary concentrations of 0.1-0.2 mg/kg, although higher

levels are often used in commercial livestock production. In 1989, the U.S. Food and Nutrition Board set Recommended Dietary Allowances (RDAs) for Se: women, 55 μg; men, 70 μg, and values for Se will be included in the forthcoming Dietary Reference Values.

3. Selenium in Food Systems

3.1. Fundamental Importance of Soil Selenium

Selenium enters soils primarily as a result of the weathering of Se-containing rocks, although volcanic activity, dusts (e.g., in the vicinity of coal burning), Se-containing fertilizers, and some waters can also be sources. Some parts of the world (e.g., Denmark, eastern Finland, New Zealand, eastern and central Siberia, and a long belt extending from northeast to south-central China including parts of Heilongjiang, Jilin, Liaoning, Hebei, Shanxi, Shaanxi, Sichuan and Zhejiang Provinces and Inner Mongolia) are notable for having very low amounts of Se in their soils and, therefore, their food systems. Other areas (e.g., the Great Plains of the USA and Canada; Enshi County, Hubei Province, China; and parts of Ireland, Colombia and Venezuela), in contrast, are seleniferous. For example, soils derived from the Se-rich Niobara and Pierre shales of North Dakota contain as much as 90 ppm Se, while most non-seleniferous soils based on low-Se granites and metamorphic sandstone contain appreciably less than 2 ppm Se. The biogeochemical mapping of Se has only been accomplished for the United States and parts of Canada and China, as well as for parts of Europe, the former Soviet Union, New Zealand and Australia (see *Agronomic Approaches to Increase Selenium Concentration in Livestock Feed and Food Crops*).

3.2. Selenium Cycle

Selenium cycles through the food system, being removed from soils by plants and soil microorganisms, which can take up the element into their tissue proteins and metabolize some of it to volatile forms (e.g., dimethylselenide). The latter enter the atmosphere to be brought down with precipitation and airborne particulates. The mobilization of Se from soils is influenced by soil pH: alkaline conditions favor the conversion of inorganic Se to selenate [Se^{+6}] which is not fixed in the soils; whereas acidic conditions favor Se^{+4} which is adsorbed to clays and is strongly fixed by iron hydroxides. Selenium is most available to plants under conditions of low precipitation and low soil leaching. This means that the availability of soil Se to crops can be affected by such soil management procedures as irrigation, aeration, liming and Se-fertilization (see *Agronomic Approaches to Increase Selenium Concentration in Livestock Feed and Food Crops*).

3.3. Selenium in Plant Materials

The Se contents of foods vary according to the amounts of available Se in soils. For example, whole wheat grain may contain more than 2 ppm Se (air-dry basis) if produced in the Dakotas, but as little as 0.11 ppm Se if produced in New Zealand, and only 0.005 ppm Se if produced in Shaanxi Province, China. On a global basis, foods with the lowest Se contents are found in the low-Se regions of China: the provinces of

Heilongjiang, northern Shaanxi and Sichuan. Ironically, foods containing the greatest concentrations of Se have also been found in China, although in different locales with local pockets of selenotic conditions.

3.4. Selenium in Animal Products

Food animals raised with feeds of low-Se content deposit relatively low concentrations of the mineral in their edible products, while animals raised with high Se nutriture yield food products with much greater Se concentrations. Due to the needs of livestock for Se to prevent debilitating deficiency syndromes, Se (usually in the form of Na_2SeO_3) is used as a feed supplement in animal agriculture in many parts of the world. This practice became widespread in North America and Europe within the last 25 years and has reduced what would otherwise be a stronger geographic variation in the Se contents of animal food products. Within the normal ranges of Se-supplementation of livestock diets, muscle meats from most species tend to contain 0.3-0.4 ppm Se (fresh weight basis). Organ meats usually accumulate greater concentrations of Se; the livers of most species generally contain about four times as much Se as skeletal muscle, and the kidneys of steers, lambs and swine have been found to accumulate 10-16 times the amounts in muscle.

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Biographical Sketch

Dr. Combs Director of the USDA Human Nutrition Research Center in Grand Forks, ND. He is also a Professor of Nutrition in the Division of Nutritional Sciences, Cornell University, Ithaca, New York, and an Adjunct Professor in the Department of Biochemistry and Molecular Biology in the University of North Dakota School of Medicine and Health Sciences. His research focuses on the nutritional biochemistry of vitamins and minerals, particularly selenium and vitamin E. He teaches graduate courses on vitamins and minerals and has a strong interest in the links between agriculture, food systems and health. He and colleagues demonstrated the efficacy of nutritional supplements of selenium in reducing cancer risks in non-deficient adults. He has published 11 books, some 330 papers and has presented more than 275 invited lectures in some 28 countries.