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Selenium compounds in medicine and nutrition

ABSTRACT

Selenium plays an important role in human nutrition and disease management. The article surveys current status on this evolving field of intense activity.

Selenium has had a vibrant but fluctuating biological history (1). While some early studies wrongly branded selenium as carcinogenic, latter studies proved selenium conclusively as toxic element. While importance of selenium as an essential micronutrient was instantly realized, it was not until 1973 when the important discovery that selenium was an essential part of the active site of the anti-oxidant enzyme glutathione peroxidase (GPx) further consolidated selenium's position in health care. US FDA approved selenium for use as a micronutrient in animal feed shortly thereafter. Selenocysteine tRNA was discovered in 1982 followed by discovery of its genetic code for incorporation into the body proteins. Essentiality of selenium for human health with RDA of 55 μg/day was established in 1989.

SELENIUM BIOCHEMISTRY AND PHARMACOLOGY

Selenocysteine, SeCys, the 21st natural mammalian proteinogenic amino acid, is the selenium analog of its sulfurous amino acid, Cysteine. There are fundamentally five distinguishing chemical characteristics between selenium and sulfur amino acids, and of course related compounds. These five factors account for the observed profound difference in the respective biological properties between the compounds containing selenium and sulfur. First the acidity of selenol group (-SeH) is a few orders of magnitude higher than its thiol (-SH) counterpart. Thus the pKa(SeH) value of SeCys is 5.2 compared to the pKa(SH) value of 8.3 for the thiol counterpart in Cysteine (2). Secondly the selenium compounds are more nucleophilic than their sulfur counterparts compared. Thirdly the redox properties of selenol/selenium compounds are also different from the corresponding sulfur functionality. Qualitatively speaking selenols are oxidized with more facility than thiols. The significant difference in redox potential of about 250mV between Selenocysteine/Selenocystine (the oxidized dimer with -Se-Se- bond) pair and Cysteine-Cystine pair points to the much more powerful reducing capabilities of SeCys (3). Fourthly, probably least investigated and understood, are the much stronger hydrogen-bonding interactions between selenoxide-hydroxyl group interactions than the corresponding sulfoxide-hydroxyl group. These hydrogen-bonding interactions may account for the substantial difference between the oxidized form of selenium containing proteins with other enzymes. Also the interaction between selenium in selenenic acid (that may be transiently produced in enzymes containing SeCys) and oxygen atoms present in enzymes may play a vital role in conformational changes. A remarkable consequence of such hydrogen bonding properties is the isolation of chiral seleninic acids in solid and solution states (4). Lastly, the longer bond-lengths found in selenium containing compounds than the corresponding bond-lengths in the sulfur counterparts may contribute to geometric flexibility and approach in protein-protein interactions. Compared to about 140g of sulfur normally found in the anatomy of adult human being, the total quantity of selenium present as part of biological molecules in human body may not exceed a few milligrams. *Still selenium wields powerful influence on body biochemistry.*

L-Selenocysteine (SeCys) has its own genetic machinery in human and bacterial cells. Interestingly free SeCys is not incorporated into selenoproteins. At first serine is hooked onto Sec-tRNA which is then converted to Sec (SeCys) while the amino acid is still bound to tRNA; Therefore the SeCys tRNA is referred to as $tRNA^{[Ser]Sec}$. The conversion tRNA bound serine or its O-phosphate involves the use of selenophosphate formed by selenophosphate synthase, itself a selenoprotein. Further incorporation into specific selenoproteins involves the UGA codon on the mRNA and a special structure referred to as SECIS element (SeCys insertion sequence). This unique genetic mechanism is different from all other amino acid insertion onto proteins. Selenium exerts its biological activity in four different forms: as Selenoproteins (5), as selenium containing proteins, as bound selenium forms and lastly as small molecules incorporating selenium. Of these four forms, extensive research data is available on selenoproteins and small molecule selenium compounds. Selenoproteins by definition contain SeCys in their active site; Selenium containing proteins may incorporate, for example, L-selenomethionine in place of methionine which may or may not have functional differences between the native and modified forms. As an example of bound selenium forms, one could cite Glutathione-Se-S-Glutathione, as also post-translational binding of selenium as a cofactor; Finally the small molecules provide the most abundant variety of different selenium compounds. They are both man-made and occur naturally also, mostly in plants. Selenium occurs predominantly as small molecules in plants where selenium enters the sulfur assimilation pathway. For example inorganic selenate directly competes with sulfate for uptake by plants (6). Yeast and mushrooms contain variety of selenium compounds in them. Bacteria also contain selenoproteins such as formate dehydrogenase. There are at least 25 genetically determined human selenoproteins. The functional aspects of all the selenoproteins are not well understood at the present time. Not all the human selenoproteins are equally fully expressed under starvation conditions of

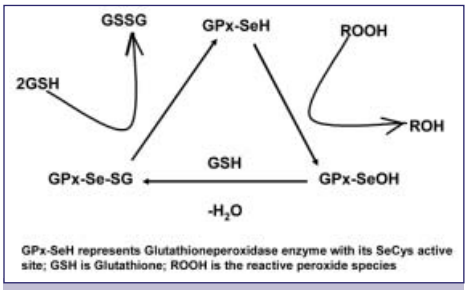

Figure 1. Schematics of the Scavenging Actions of CPx

selenium supply. Similarly there exists a hierarchy among tissues/cells for placing their demands on the available selenium supply apparently brain being among the top of the contenders.

We shall discuss very briefly the major human selenoproteins and their so-far known functions. Glutathione peroxidase(s) (GPx) was already mentioned as the first human selenoprotein identified and probably most widely studied. They are anti-oxidant enzymes detoxifying reactive free radicals and peroxycompounds. Up to seven isoenzymes have been identified so far. The second type of selenoenzymes comprises the class of deiodinases that are involved in cleaving specific carbon-iodine bonds in thyroid hormones thereby regulating their activity. Three such iodothyroninedeiodinases are known. The third enzyme, Selenoprotein P rivals GPxs in its abundance. There are about 10 SeCys residues per enzyme molecule. Its main function seems to be a carrier of nutritional selenium from plasma to peripheral organs. The fourth enzyme selenophosphate synthases (only one contains SeCys) are involved in transforming t-RNA bound serine to bound SeCys. Thioredoxin reductases, three of them are known, mediate the reduction thioredoxin using NADPH (7). Other notable selenoproteins, Selenoprotein N and W, are believed to have essential functions in muscle cells.

Nutritional selenium performs useful functions fundamentally in three different ways.

Firstly it is believed that nutritionally supplied selenium metabolizes to a selenide equivalent which is assimilated by the genetic machinery as SeCys into the functionally important various selenoproteins described earlier.

It is also believed that some of the molecules such as methylseleninic acid, Se-methyl-L-selenocysteine etc breakdown to a selenium intermediate with a single carbon, equivalent to a methylselenol, which by itself exerts therapeutic function, especially anticancer effects.

Thirdly compounds like Ebselen, Se-Methyl-L-selenocysteine etc may mimic the enzymatic functions such as those of GPx thus minimizing the demand on such enzymes engendered by oxidative stress conditions.

SELENIUM COMPOUNDS AS ANTIOXIDANTS

Considerable literature is extant on the role of selenium compounds as antioxidants. This relates to the ability of small molecule selenium compounds to mimic the action of glutathione peroxidase (GPx). Cells contain several antioxidant enzymes including GPx which act as scavengers of reactive oxygen species such as peroxides and reduced oxygen species that contribute to oxidative stress. Since oxidative stress has been implicated in a variety of disease states, a successful GPx mimic is a much sought after target (8). The catalytic cycle of GPx is shown in Figure 1; GPx, a SeCys containing enzyme in its active site, reacts with peroxides to convert them to innocuous products through the sacrifice of two molecules of glutathione. It is the redox properties alluded to be associated with SeCys moiety that is responsible for the enzymatic action. Gpx mimics include Ebselen and L-Se-methylselenocysteine, the former one being totally synthetic and the latter one occurring naturally in several edible plants including garlic. Such small selenium compounds mimicking GPx occupy the central place of GPx shown in Figure 1, thus playing a major role in alleviating oxidative stress conditions (9). Structures of some more extensively investigated selenium containing compounds from the biological angle are shown in Figure 2.

CHEMOPREVENTION AND THERAPY OF VARIOUS CANCERS

It was pointed out that the RDA for selenium is 55 μg per day. Clark et al (10) found that a group supplemented with 200 μg/day of Selenium exhibited significantly lower incidences of cancer mortality/rate with specific cancers of the prostate, lung and colon/rectum. The extraordinary results obtained by Clark et al sparked off an abiding interest in selenium-cancer connection. It has been generally agreed that selenoproteins are indeed involved in minimizing the risk of incidence of cancer and that selenium supplementation increases selenoprotein expression. In addition to these selenoproteins, certain methylated selenium metabolites such as methyl selenol also play a role in anti-cancer effects both at progressive and metastasis stages. A metabolite such as methylselenol may arise from Se-methyl-L-selenocysteine or its glutamylated form γ-L-glutamyl-Se-methyl-L-selenocysteine (11). The enzyme β-lyase has been implicated in the metabolism (12). It was also demonstrated that methylseleninic acid is also an effective agent for chemoprevention. It might again serve as precursor for methylselenol and may not need enzyme β-lyase for producing the active metabolite (13). Anticancer activity of L-selenomethionine can also be attributed to its metabolism to methyl selenol or its contribution to the expression of several selenoproteins again through metabolism (14).

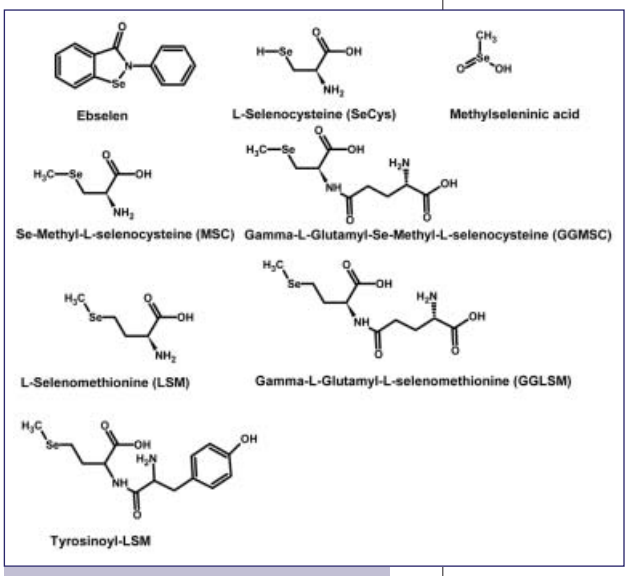

Figure 2. Structures of some synthetic and naturally-occuring selenium compounds

Since many of these small selenium containing molecules mediate cancer prevention and propagation in various ways, an interesting concept of using these substances together in product such as a "selenium cocktail" approach can be adopted. It has been known that plants such as garlic do contain L-selenomethionine, Se-methyl-selenocysteine, γ-L-Glutamyl-L-selenomethionine, γ-L-Glutamyl-Se-methyl-L-selenocysteine among their selenium repertoire. Indeed experimental evidence points to the cancer-preventive properties of garlic and other plant materials (15). Standardized extracts of garlic hydroponically grown in the presence of selenium have been reported (16). Certain forms of selenium compounds such as Se-methyl-L-selenocysteine are more efficacious

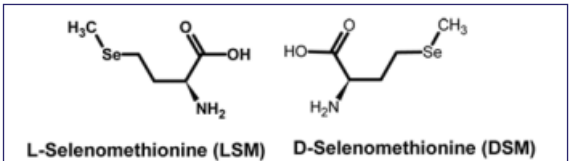

Figure 3. Structures of Stereoisomers of Selenomethionine

for mammary cancer prevention than other selenium compounds (17). One of the largest clinical trials called SELECT to evaluate selenium for prostate cancer prevention is on-going using pure L-selenomethionine (18). Another exciting development is the on-going research on the use of anti-cancer compounds given along with small molecule selenium compounds such as Se-methyl-L-selenocysteine and L-selenomethionine (19).

ANTIVIRAL EFFECTS AND IMMUNE ENHANCEMENT

Deficiency of selenium status in the host increases its susceptibility to viral infections. Also it has been demonstrated that viruses, normally non-virulent in a selenium sufficient-host, become irreversibly virulent when the host is in selenium deficient state (20). Obviously these observations have a bearing on HIV, influenza and bird-flu virus.

OTOPROTECTION

Selenium containing compounds are being investigated for Noise-induced Hearing Loss (NIHL), a leading occupational disease and a major contributor to the development of age-related hearing loss (21).

HYPOTHYROIDISM

Selenoproteins, iodothyronine deiodinases are involved in thyroid hormone (22). Combined selenium/iodine deficiency leads to cretinism in infants.

MUSCULAR DYSTROPHY

Deficiency in two selenoproteins, N and W, has been linked to muscular Dystrophic conditions (23).

AGE RELATED COGNITIVE DECLINE AND ALZHEIMER

Research has indicated a decrease in their plasma selenium level with higher the probability of cognitive decline (24). A part of the SELECT trial, PREADVISE evaluates the effect of selenium and Vitamin E on the incidence of Alzheimer's disease (25).

HEAVY METAL POISONING

Protective effect of selenium against mercury and arsenic poisoning has been well recognized (26).

RAS (RESPIRATORY ANCILLARY STUDY)

The overall objective of RAS is to understand whether selenium and Vitamin E impact the loss of lung function experienced with age. The participants are again a subset of SELECT trial participants (27).

CATARACTS AND AMD

Selenium deficiency is purported play a significant role in two of the leading eye diseases, namely, cataract (28) and Age Related Muscular Degeneration (27) affecting especially older population.

TOPICAL APPLICATIONS

Use of L-selenomethionine for avoiding ill-effects of UV rays has been demonstrated (29). Selenium sulfide has been in use in shampoo applications.

CHIRALITY ISSUES IN SELENIUM SUPPLEMENTATION

It has been found that while L-selenomethionine is absorbed and metabolized, its enatiomer, D-selenomethionine seems to be excreted essentially as unchanged (30). Hence, when chiral selenium compounds are used as supplements or drugs, chiral purity is a crucial issue. If this aspect of stereochemistry is ignored, vitiated conclusions will be obtained.

CONCLUSIONS

Organic selenium compounds, as sources of selenium, have been found to be more bio-available for the expression of selenoproteins than inorganic selenium for nutritional and medicinal applications (31, 32).

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