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Selenium - its role in physiology and endocrinology and as organoselenium compounds in oncology: A minireview

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The present minireview traces the road leading to discovery of selenium, formerly appointed as a toxic element that became later a bioelement, which is necessary for the proper functioning of living organisms. Selenium occurs in human and animal bodies either in the form of seleno-L-cysteine or its dimeric form seleno-L-cystine as a crucial component of selenoenzymes or selenoproteins. Selenium atom represents an integral component of the enzyme active site of different forms of glutathione peroxidase, which catalyzes conversion of hydrogen peroxide and organic hydroperoxides into the water and corresponding alcohols. A revolutionary breakthrough in the field of endocrinology came with the identification of different forms of iodothyronine deiodinase as selenoenzymes, which play an important role in the metabolism of thyroid hormone. The role of selenium in immune function and autoimmune thyropathies that might be associated with selenium deficiency are reported and discussed. This minireview also brings forward novel directions of organoselenium compounds or selenium nanoparticles in cancer therapy. Based on the update of available literature and the author's experimental experience, the minireview can be devoted to clinicians and medical students.

Keywords: selenium, organoselenium compounds, selenium nanoparticles, selenoenzymes, selenoproteins, thyroid hormone, immune function, autoimmune thyropathies, cancer

Selenium was discovered by the Swedish chemist Jons Jacob Berzelius at Stockholm in 1817 and this new chemical element has been named after the Greek goddess of the Moon, Selene. In the first half of the last century, selenium was considered as an undesirable and toxic element mainly for higher organisms and mammals and its toxicity was markedly identified as a cause of livestock poisoning (Brtkova and Brtko 1996). Some plant species, members of the genera Astragalus in several regions of the USA (California, South Dakota, Nebraska), are capable to accumulate selenium from seleniferous soil (Se >100 mg Se/kg dry plant tissue). These plants were considered to be selenium accumulators. Some species of plants in Colorado (Astragalus bisulcatus) or Wyoming (Astragalus racemosus) can even accumulate selenium from seleniferous soil up to 15000 mg/kg dry plant tissue and therefore, they are called selenium hyperaccumulators (White 2016). On the other hand, an appearance of these plants may indicate the presence of seleniferous soil in nature (Oldfield 1987).

A remarkable breakthrough in the field of selenium element investigation came in the second half of previous century. A marked change of mind has taken place on the importance of selenium for the normal function of higher vertebrates. A new chapter in the field of selenium and its role as a principal biological trace element was opened in 1951 by Schwarz and Foltz (1999), who have reported that

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selenium is able to prevent liver necrosis in animals consuming vitamin E deficient diet. This finding confirmed selenium bioactivity and suggested the existence of selenoproteins and/or selenoenzymes and their involvement in the metabolism of higher vertebrates. Selenium occurs both in prokaryocytes and eukaryocytes as a component of selenoenzymes or selenoproteins and almost 80% of selenium atom in human or animal body occurs in the form of seleno-L-cysteine (Brtkova and Brtko 1996).

Basic pathways of selenium metabolism, a biologically important metalloid element, which are similar to those of sulfur, have been reviewed elsewhere (Foster and Sumar 1997; Ganther 1999; Kohrl et al. 2000; Kohrle 2005, 2023). This minireview summarizes the general characteristics of important biologically active selenoenzymes and other selenoproteins and also introduces possible employment of novel organoselenium compounds as antitumor preparations in clinical oncology.

Selenoenzymes glutathione peroxidases and selected selenoproteins

Selenium atom represents an integral component of the enzyme active site of glutathione peroxidase, which catalyzes conversion of hydrogen peroxide and organic hydroperoxides into the water and corresponding alcohols (Flohe et al. 1973; Rotruck et al. 1973). Selenium together with vitamin E play an important role as a component in the antioxidant defense system. Classical four disparate glutathione peroxidases functioning in distinct subcellular compartments require selenium atom at the active site of the enzyme subunit as a seleno-L-cysteine residue (Arthur et al. 1987). Cytosolic glutathione peroxidase (cGSH-Px or GPx-1) is predominantly present in erythrocytes and several other tissues. It is a tetrameric protein containing four identical and spherical subunits, which are arranged in an almost square planar configuration with one atom of selenium per subunit of the enzyme (Epp et al. 1983). Gastrointestinal glutathione peroxidase (giGSH-Px or GPx-2) properties and the protein structure have been found to be very similar to those of cGSH-Px. Its expected role might be in protecting mammals from the toxicity of ingested lipid hydroperoxides (Chu et al. 1993).

Plasma glutathione peroxidase (plGSH-Px or GPx-3) is an extracellular enzyme, which differs from cGSH-Px both in the structure and site of function. It is a tetrameric glycoprotein with four atoms of selenium per enzyme molecule (Maddipati and Marnett 1987). Phospholipid hydroperoxide glutathione peroxidase (PGSH-Px or GPx-4) is closely associated with intracellular membranes and in contrast to other glutathione peroxidases, it is a monomer with one atom of selenium per enzyme molecule (Arthur and Beckett 1994; Brtkova and Brtko 1996). Glutathione peroxidase 5 (GPx-5), also known as epididymal secretory glutathione peroxidase, is an enzyme that also belongs to the glutathione peroxidase family. It is predominantly expressed in the epididymis in the mammalian male

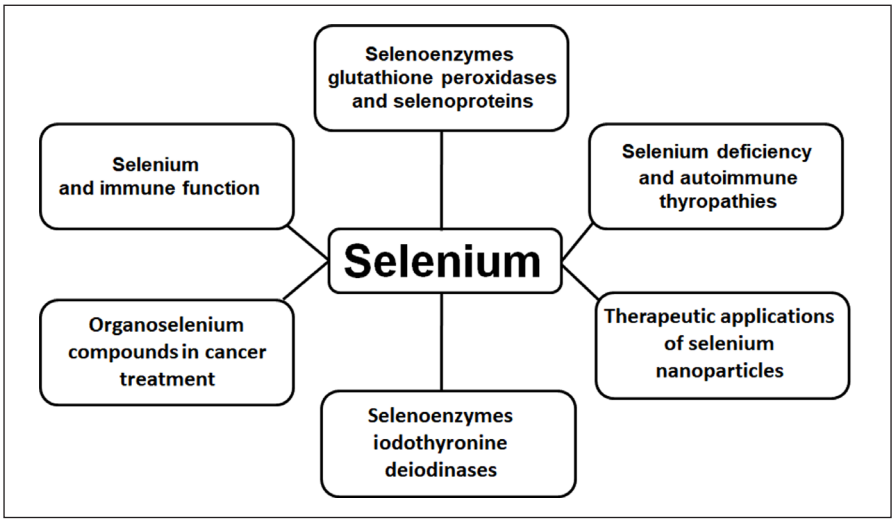

Figure 1. Schematic outline of selenium involvement in different human body functions and diseases.

reproductive tract and is androgen-regulated (Hall et al. 1998). Similarly, male glutathione peroxidase 6 (GPx-6), which is also a member of the GPx family, is attached to the sperm head preventing the sperm to undergo premature capacitation by affecting components of the antioxidant pathway (Chen et al 2020).

Selenoprotein P, which is synthesized in liver, is a single protein containing 10 seleno-L-cysteine residues (Read et al. 1990). Since, almost 60–80% of the plasma selenium is associated with the selenoprotein P molecules, the selenoprotein P is considered to be a main selenium transport protein, which is responsible for selenium transfer from liver to other tissues (Zachara 1992).

Mitochondrial capsule selenoprotein (MCS), which is vital to the integrity of sperm flagella, has been shown to be a structural protein of the mitochondrial sheath in spermatozoa and is mainly related to the spermatogenesis (Nam et al. 1998; Holben and Smith 1999). Selenoprotein W (SeW) is a small selenoprotein (85 to 88 amino acids), which serves as an antioxidant responding to stress and is involved in the cell immunity and thioredoxin-like function (Whanger 2009). Mammalian selenocysteine-containing thioredoxin reductase provides reducing power for several biochemical processes and defends against oxidative stress. Selenophosphate synthetase is an enzyme required for the incorporation of selenocysteine into selenoproteins (Holben and Smith 1999).

Role of selenium in synthesis and metabolism of thyroid hormone

Enzymes of glutathione peroxidase family are known to defend the thyroid gland against continuous hydrogen peroxide production and control the biosynthesis of thymoglobulin molecules, the product of thyroid follicles, which is an essential protein for biosynthesis of thyroid hormone, its storage, and secretion (Flohe et al. 2022; Kohrle and Fradrich 2022; Kohrle 2023).

A revolutionary breakthrough in the field of endocrinology came with the identification of type I iodothyronine 5'-deiodinase (D1) as a selenoenzyme consisting of two identical subunits with one atom of selenium per subunit of 27 kDa in active site functioning as a dimer (55 kDa) in a phospholipid environment (Arthur et al. 1990; Behne et al. 1990). In general, deiodinases catalyze the reductive cleavage of aromatic "C–I" bonds in ortho position to either a phenolic or a diphenyl ether oxygen atom in iodothyronines (Kohrle et al. 2005). D1 catalyzes the 5'-deiodination of L-thyroxine (T4), reverse 3,3',5'-triiodo-L-thyronine (rT3), and other iodo-L-thyronines or their sulfoconjugates with the highest abundance in liver, kidney, thyroid, and pituitary of adult higher mammals (Kohrle 2002). The type II, iodothyronine 5'-deiodinase (D2) represents the second selenoenzyme of the deiodinases family involved in monodeiodination of T4 (prohormone) to 3,3',5-triiodo-L-thyronine (T3), the biologically active thyroid hormone. D2 has been found to be highly expressed in the central nervous system with the highest concentrations in glial cells and tanycytes (Guadano-Ferraz et al. 1997). Type III, iodothyronine 5-deiodinase (D3), which is expressed in many tissues, is the third important selenoenzyme responsible for the catalysis of T4 and T3 inactivation process. Its main role is to control active thyroid hormone levels in organisms (Kohrle et al. 2005).

Selenium and immune function

The supplementation with selenium, even in individuals without deficit of this micronutrient, has significant immune stimulatory effects including: improvement in the proliferation of activated T cells, elevation in tumor cytotoxic lymphocyte-mediated toxicity, and increase of natural killer (NK) cell activity. Selenomethionin inhibits interferon gamma (IFN-γ), tumor-necrosis factor α (TNF-α) and interleukin 2 (IL-2). Studies performed in selenium deficit mice have shown reduced amount of mature and functional T cells, as well as their failure to suppress the production of oxygen free radicals followed by suppression of T cell proliferation. T cells are sensitive to oxidative stress and T cells with deficit of selenoproteins cannot proliferate in response to the stimulation of their receptors. Suppressor T lymphocytes are notable to inhibit sufficiently the production of IL-2. That is the cause of stimulation of autoreactive T-lymphocytes production. Selenium deficiency and reduced Gap activity in lymphocytes contribute to the development of autoimmunity (Duntas 2015; Duntas and Benvenga 2015; Ventura et al. 2017).

Diseases that might be associated with selenium deficiency

Keshan disease is an endemic cardiomyopathy that in the former centuries primarily affected children and adolescents in low soil selenium areas of China. This disease was successfully suppressed

by supplementation of patients with 0.5–1.0 mg of sodium selenite per week (Chen et al. 1980). Similarly, Kashin-Beck disease, an endemic osteoarthritis, which occurred during the preadolescent or adolescent age of man mainly in northern China, North Korea, and eastern Siberia, was linked with iodine deficiency in association with selenium deficiency. Clinical data have shown that in areas, where severe iodine and selenium deficiency is endemic, iodine deficiency is predominantly considered to be a major risk factor for Kashin-Beck disease (Moreno-Reyes et al. 1998, 2003).

Selenium deficiency and autoimmune thyropathies

Decreased activity of GPx in lymphocytes, due to selenium deficiency, participates in the development of autoimmune diseases. Among them, autoimmune thyroiditis (AIT) is most common and we are facing the real epidemic of this chronic thyroid inflammation (Duntas 2015; Podoba et al. 1992). It is the most common organ-specific autoimmune disorder, the most common endocrinopathy and the most common cause of primary hypothyroidism in countries with sufficient iodine intake. The etiopathogenesis of AIT and Graves' disease (GD) is not up to present time sufficiently understood. It is characterized by a profound interaction between genetic and environmental factors. Oxidative stress has been implicated in the pathogenesis of both diseases. Hence the antioxidant properties of selenoproteins are relevant to the rationale for the use of selenium supplementation as the therapy in both conditions.

In a cell-culture study of orbital fibroblasts from patients with Graves's opthalmopathy (EO), incubation with selenocystein reduced fibroblast proliferation, hyaluronic acid release, and secretion of pro-inflammatory cytokines (Dottore et al. 2017). In another *in vitro* study, incubation of rat thyroid follicular cells FRTL5 with sodium selenite inhibited the expression of HLA-DR (human leukocyte antigen-DR isotype) and prevented cell apoptosis (Nettore 2017). Slightly lower serum selenium levels in patients with AIT compared to controls were reported by Wimmer et al. (2014) in Austria, however, significantly lower in Denmark, especially in GD patients, indicating a potential risk between inadequate selenium intake and overt autoimmune thyroid disease, especially GD (Bulow Pedersen et al. 2013). The same line of evidence has been published by German authors (Wertenbruch et al. 2007). Moreover, serum selenium levels were lower in GD patients with EO compared to GD patients without EO in the Australian study (Khong et al. 2014). These findings underscored the association of selenium deficiency and thyroid autoimmunity and strongly indicate that low selenium levels may be a risk factor for EO in GD patients. Since 2002, more than 20 trials have investigated the effect of selenium supplementation in AIT patients (Gartner et al. 2002; Duntas et al. 2003). Several meta-analysis studies have reported that when compared to placebo, selenium supplementation decreases anti-thyroid peroxidase (anti-TPO) antibodies concentration in patients with chronic AIT (Toulis et al. 2010; Wichman et al. 2016). On the other hand, up to present time, there is no evidence of clinical importance, such as the effect on disease remission, lowered thyroxin dose or improved quality of life. There is a question whether a decrease in anti-TPO titer alone warrants the routine use of selenium supplementation.

At the present time, there is no official recommendation for selenium supplementation in patients with AIT. Significant proportion of anti-TPO positive women will develop postpartum thyroiditis and of these 20–40% will develop permanent primary hypothyroidism. In a highly cited, randomized, placebo-controlled trial, in 151 Italian women with low selenium status, postpartum thyroiditis, and permanent hypothyroidism were significantly lower in the group treated with 200 μg selenium/day than in the placebo group (28.6% vs. 48.6% placebo group and 11.7% vs. 20.3% placebo group) (Negro et al. 2007). Similarly, in another Italian trial, in pregnant women positive for anti-TPO or anti-thyroglobulin (anti-Tg), a significant reduction in both types of antibodies has been found in selenium-treated group, whereas an antibody rebound occurred in the placebo group (Mantovani et al. 2019). In 2011 European multicenter, randomized, controlled trial, in 159 euthyroid patients with mild EO, the authors have reported improved quality of life, less eye involvement, and slower disease progression in those patients receiving selenium, i.e., benefits that persisted at the 12-month follow-up (Marcocci et al. 2011). Based on these results, the European Thyroid Association (ETA) has suggested a 6-month trial of selenium supplementation in patients with mild EO (Bartalena et al. 2016).

The use of selenium supplementation is not yet endorsed in international guidelines for the management of AIT, hypothyroidism, hypothyroidism in pregnancy or hyperthyroidism without EO. Nevertheless, 20–75% European endocrinologists prescribe selenium supplementation to patients

with AIT. There is a growing body of evidence that anti-TPO/anti-Tg positivity in euthyroid AIT patients has a negative impact on general health. Some studies have reported impaired health-related quality of life, depression, and anxiety in euthyroid patients (Giynas Ayhan et al. 2014; Yalcin et al. 2017).

Studies with several thousands of euthyroid anti-TPO/anti-Tg positive subjects showed that anti-TPO levels were positively associated with total cholesterol, triglycerides, insulin resistance, C-reactive protein concentration, blood pressure, body mass index, obesity, waist circumference, and glucose level. These studies have indicated that metabolic disorders are associated with increased thyroid autoantibodies levels (Tamer et al. 2011; Liu et al. 2018; Wu et al. 2020). These robust studies bring expectations for the evidence of the necessity of decreasing anti-TPO/anti-Tg titers for many reasons. New trials in both AIT and GD have potential to reverse current clinical practice and current guidelines.

Organoselenium compounds in cancer treatment

During several decades, a marked effort has been directed toward the synthesis of new and stable organoselenium compounds with less toxicity that might be potentially used in clinical oncology as novel antitumor preparations. Milner and Hsu (1981) have shown that selenium selenite was capable to inhibit a propagation of the mouse lymphocytic leukemia L1210 cells. Organic selenocyanate molecules have been shown as promising compounds exerting their antitumor action (Fernandes and Gandin 2015). The first selenocyanate reported, 1,4-phenylenebis(methylene) selenocyanate, has been proven to be effective against oral squamous carcinoma cells and prostate carcinoma cells (Ghose et al. 2001; Pinto et al. 2007). Two decades ago, we have prepared two selenium containing compounds, 5-benzyloxy-2-selenocyanatomethyl-4H-pyran-one and 5-methoxy-2-selenocyanatomethyl-4H-pyran-one (Rondahl et al. 2003) in order to investigate their antitumor effects in human skin carcinoma (A431) and human breast carcinoma (MCF-7) cells. Cancer cell growth inhibitory activities of the above selenium containing kojic acid derivatives have been found to be preferentially aimed at the intracellular compartment rather than the plasma membrane and thus, 5-benzyloxy-2-selenocyanatomethyl-4H-pyran-one and 5-methoxy-2-selenocyanato-methyl-4H-pyran-one enlarge the group of antiproliferative active compounds containing selenium atom in the molecule (Fickova et al. 2008). Selenodiglutathione was first tested as an anticancer agent three decades ago. However, the further studies have been stopped for its adverse side effects (Fernandes and Gandin 2015). Seleno-L-methionine and Se-methyl-seleno-L-cysteine have been tested for their ability to inhibit tumor growth of breast, prostate, colorectal, and melanoma cells; however, their antitumor activity was shown at higher concentration in micromolar range (Shin et al. 2007). Cytotoxic effects of selenocystine have also been confirmed in liver cancer cells, lung, breast, cervical cancer cells as well as in melanoma cells (Gandin et al. 2018). The antitumor effects of methylseleninic acid have been reported in human breast cancer (Qiu et al. 2019) and pancreatic cancer (Wang et al. 2014).

Many selenide or diselenide compounds have been analyzed for their antitumor actions and several of these selenium containing compounds have shown their promising antitumor activity (Fernandes and Gandin 2015). Among selenoesters, xylitolselenious ester has shown selective cytostatic effects on human hepatoma cells without affecting normal human hepatic cells (Guo et al. 2013). Arsenyan et al. (2007) have reported that several 4-methyl-1,2,3-selenadiazole-5-carboxylic acid amides exert antitumor potential both *in vitro* and *in vivo* against mouse fibroblasts 3T3 cell lines, mouse hepatoma MG-22A or human fibrosarcoma HT-1080 cells. Both 2-phenyl-1,2-benzisoselenazol-3(2H)-one, known as Ebselen or (1,2-[bis(1,2-benzisoselenazolone-3(2H)-ketone)] ethane (Ethaselen) were effective against various cancer cell lines in micromolar range (Gandin et al. 2018). Recently, it has been shown that several cobalt, cooper or zinc selenium-containing complexes, when tested in human colon cancer HCT-116 and human breast cancer MCF-7 tumor cell lines, were found to be promising for cancer treatment as they were effective in the same concentration range as cisplatin (Kostic et al. 2024).

Several isoselenocyanates have been found to be more cytotoxic toward melanoma cancer cells when compared to their corresponding sulfur containing derivatives. Among them, phenylbutyl isoselenocyanate has been found to be more potent and effective in inhibiting proliferation of UACC 903, WM115 or 1205 Lu melanoma cells than its corresponding phenylbutyl isothiocyanate (Frieben et al. 2019). Our recent data have shown that the selenium derivative of triorganotin compound, newly synthesized triphenyltin isoselenocyanate, exerted higher cytotoxicity in nanomolar range in human, hormone sensitive, breast

cancer MCF-7 cell line (IC50: 250 nM) in comparison with triple-negative MDA-MB-231 breast carcinoma cell line (IC50: 450 nM). Triphenyltin isoselenocyanate has been found to exert DNA damage-linked antineoplastic activity in breast carcinoma cell lines (Hunakova et al. 2022). Our data have also shown that triphenyltin isoselenocyanate, a novel selenium atom containing derivative of triorganotin origin, represents a new cognate bioactive ligand for nuclear retinoid X receptors. The data have also shown that triphenyltin isoselenocyanate induces apoptosis via a caspase cascade triggered by the mitochondrial apoptotic pathway (Macejova et al. 2024).

Possible therapeutic applications of selenium nanoparticles

Selenium nanoparticles (SeNPs) are gaining great popularity due to their high permeability and low or no toxicity. They might be successfully used in the targeted delivery of drugs as anticancer or anti-inflammatory agents (Jolly et al. 2020). SeNPs penetrate cells through endocytosis and are capable to deliver differently charged macromolecules and antitumor agents at a nanoscale, and thus exhibit their high antitumor activity (Ansari et al. 2024). Varlamova (2024) has described the molecular mechanism of the cytotoxic effect of SeNPs of various origins on hepatocellular carcinoma cells. In general, it is based on a dose-dependent generation of various calcium signals, enhancement in the expression of a number of pro-apoptotic genes, including GADD34, BAK, BAX, PUMA, CASP-3, and CASP-4, and activation endoplasmic reticulum stress through the protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) signaling pathway. A comprehensive examination of different synthesis techniques has been thoroughly reviewed by Sampath et al. (2024). Recently, SeNPs have been demonstrated to affect autophagy allowing the SeNPs to employ directly as anticancer agents (Ali et al. 2024). On the other hand, the stability and functionality of SeNPs during the storage process can be affected by various environmental factors including temperature, ionic strength, and pH, but surface functionalization may improve the storage stability of SeNPs (Chen et al. 2022). SeNPs can be produced either by physical and chemical processes or by biogenic synthesis, which is an eco-friendly that is non-toxic to humans and animals (Ullah et al. 2022).

Conclusion

In spite of the fact that a number of biologically active derivatives containing selenium atom(s) in their molecules are known, future biological studies on new organoselenium compounds and/or involvement of SeNPs in cancer treatment may lead to the development of effective and specific pharmaceutical preparations applicable in human or veterinary medicine.

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