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REVIEW PAPER

BIOMEDICAL EFFECTS OF SELENIUM IN A HUMAN ORGANISM*

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Abstract

Selenium, an essential nutrient in a human diet, can be administered in both organic and inorganic forms. Organic forms are easier to ingested than inorganic ones. The biological functions of selenium are mediated largely by selenoproteins. Selenium is present in mammalian selenoproteins as selenocysteine. Human selenoproteins encoded by 25 genes are involved in glutathione-dependent hydroperoxide removal, reduction of thioredoxins, selenophosphate synthesis, activation and inactivation of thyroid hormones, repair of oxidized methionine residues, and ER-associated protein degradation. These functions are responsible for the role of selenium in human health, including its pro- and anticancer activities, roles in the immune system, and other functions. Selenium is regarded as a controversial trace element. Its deficiency is associated with cancer, cardiovascular diseases, infertility, thyroid diseases and poor immune functions. On the other hand, selenium in high levels has been considered as a poison, causing symptoms such as memory loss, fatigue, diarrhoea and vomiting, in addition to which it can increase the risk of type 2 diabetes and cancer. There are many aspects of the metabolism of selenium and selenoproteins that remain to be investigated. The purpose of this article is to bring up to date the current status of the developing field of selenium research, centered around the health benefits attributed to this element. The relationship between the selenium status in a human organism and selected health outcomes is discussed.

Keywords: selenium, metabolism, selenoproteins, health effects, supplements.

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INTRODUCTION

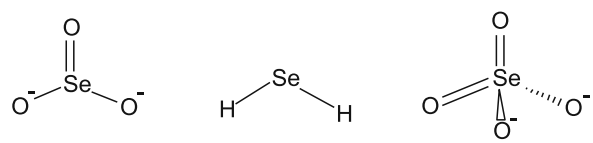
In 1957, selenium (Se) was recognized as an essential micronutrien (Schawrz, Foltz 1957). Selenium is incorporated into proteins (selenoproteins) in a co-translational mechanism as the 21st amino acid, selenocysteine (Sec). Selenoproteins have several functions, including selenium homeostasis and transport, thyroid hormone metabolism, antioxidant defence, anti-inflammatory action and cardiac and skeletal muscle metabolism (reviewed in ref. Frączek, Pasternak 2013, Mehdi et al. 2013, Hatfield et al. 2014).

Selenium is regarded as a controversial trace element. Selenium deficiency is associated with cancer, cardiovascular disease, infertility, thyroid disease and poor immune function. On the other hand, selenium in high levels has been considered as a poison, causing symptoms such as memory loss, fatigue, diarrhoea and vomiting (reviewed in ref. Navarro-Alarcon, Cabrera-Vique 2008, Frączek, Pasternak 2013).

The purpose of this article is to bring up to date the status of the developing field of selenium research centered around the health benefits attributed to this element We discuss the relationship between the selenium status in a human organism and selected health outcomes.

SOURCES, METABOLISM AND DISTRIBUTION OF SELENIUM COMPOUNDS

Selenium exhibits valences of (II), (IV), and (VI). It is present in both inorganic (Figure 1) and organic compounds (Figure 2).



a *b* *c*

Fig. 1 Structures of inorganic selenium-containing compounds: selenite (Se(IV)) – *a*, selenide (Se(II)) – *b* and selenate (Se (VI)) – *c*

In living organisms, both organic and inorganic compounds containing selenium are metabolized. Figure 3 presents metabolic pathways of selenium-containing compounds in the human organism.

Bioavailability of selenated organic compounds is much higher than that of inorganic compounds (Thomson 2004). The absorption of Se-species occurs by different mechanisms mainly in the lower part of the small intestine. The efficiency of absorption of inorganic and organic selenated compounds is almost complete (70-90%) under physiological conditions. The exception

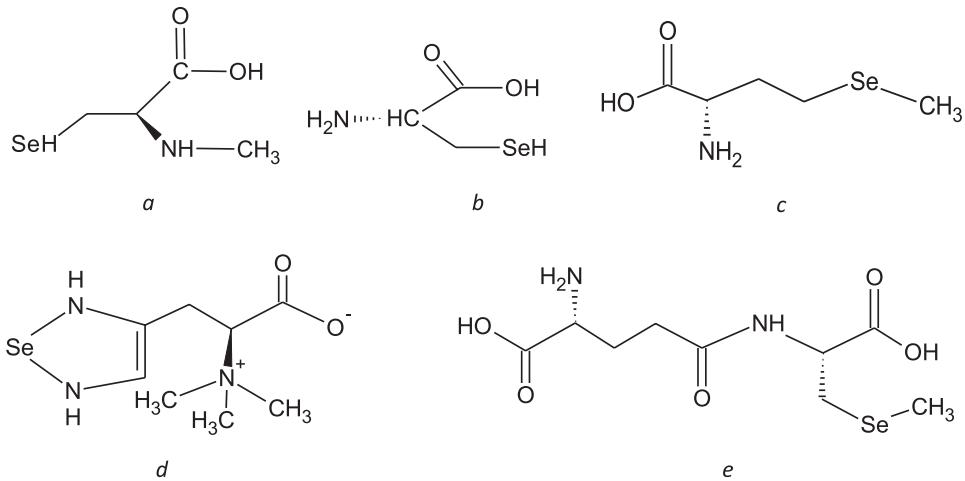


Fig. 2. Organoselenium compounds (Se(II)): Se-methylselenocysteine (SeMeSec) – *a*, selenocysteine (Sec) – *b*, selenomethionine (SeMet) – *c*, 2-selenyl-$N_\alpha N_\alpha N_\alpha$-trimethyl-L-histidine (selenoneine) – *d*, γ-glutamyl-Se-methylselenocysteine (GGSeMeSec) – *e*

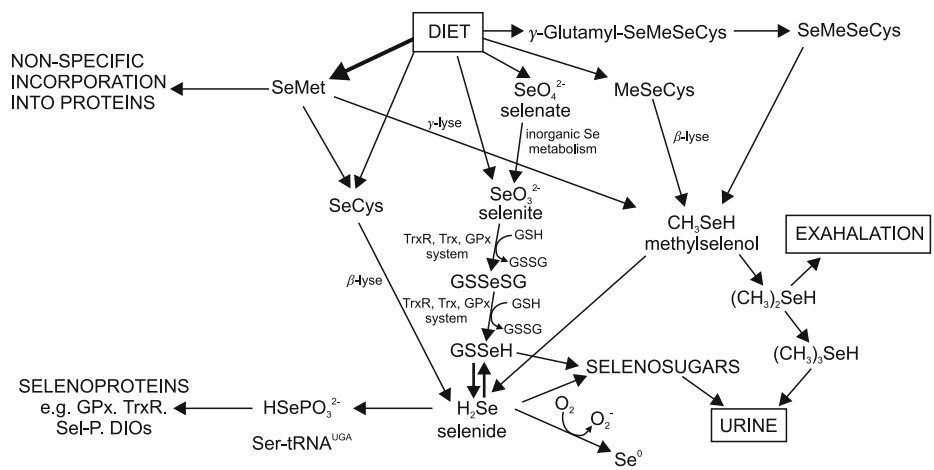


Fig. 3. Metabolic pathways of selenium in the human organism. Adapted from WEEKLEY et al. (2013)

is selenite absorption which does not exceed 60%. However, its absorption is increased in the presence of reduced glutathione (GSH) in the gastrointestinal fluid. The absorbed fraction of selenite is reduced to selenodiglutathione (GSSeSG) by GSH, thioredoxin reductase (TrxR), thioredoxin (Trx), and glutaredoxin (Grx) systems. GSSeSG is subsequently transformed to hydrogen selenide (HSe^-). In this form, selenium can be directed to the metabolic pathways leading to the synthesis of selenosugars or selenoproteins. Hydrogen selenide can also be metabolized into selenium in its 0 oxidative state (WEEKLEY 2013).

Selenate is actively absorbed by a Na^+-dependent transport system like sulphate. Then, it is reduced by ATP sulfurylase to selenite. After this process, the metabolic pathway for selenate is the same as for selenite (Mataix Verdu, Llopis 2002).

Selenium incorporated into amino acids undergoes different metabolic processes. Selenomethionine is absorbed by the same Na^+-dependent neutral amino acid transport system used by methionine. On the other hand, selenocysteine and selenite are not absorbed by active transport and their capture is not inhibited by similar sulphur compounds as well as by selenium status in the organism (Mataix Verdu, Llopis 2002). Selenomethionine can be metabolized through three different pathways: (1) directly non-specifically incorporated into Se-containing proteins, (2) metabolised to selenocysteine or (3) degraded to methyl selenol ($MeSe^-$) by γ-lyase (Brozmanová et al. 2010). Methyl selenol can also be formed *via* SeMeSeCys from γ-glutamyl-Se--methylselenocysteine (γ-glutamylSeMeSeCys) found in plants.

In humans, methylselenocysteine is changed by *β*-lyase to methyl selenol, which can be metabolized to selenide (HSe^-). It is next methylated to di- and trimethylselenium ion. Selenide is the common point for regulation of selenium metabolism in the human organism due to the fact that different forms of selenated compounds are metabolized into it. Under a low-toxic selenium status, selenide is converted on a major excretory pathway which is the formation of selenosugars: Se-methyl-N-acetyl-galactosamine (MSeGalNAc), Se-methyl-N-acetyl-glucosamine (MSeGluNAc), and Se-methyl-N-amino--galactosamine ($MSeGalNH_2$) excreted in urine (Kobayashi et al. 2002).

When selenium intake is excessive, dimethylselenide may occur in the breath and the trimethylselenonium ion may occur as a minor metabolite in urine (Francesconi, Pannier 2004). Faecal excretion is also the path of selenium elimination. A low amount of selenium is lost through the skin. Both, biotransformation in the liver and excretion represent a major mechanism by which selenium homeostasis is maintained during excessive exposure (Mataix Verdu, Llopis 2002). The selenium requirement to compensate for minimal losses in humans is 50-70 μg/day (Alexander, 2015).

SELENOPROTEINS

Selenium is incorporated as selenocysteine into at least 25 selenoproteins encoded by the human genome (Rayman 2012, Gladyshev et al. 2016). Selenocysteine is found in the active centre of a number of selenoprotein enzymes (Lu, Holmgren 2009). The majority of selenoproteins catalyze oxidation-reduction reactions, particularly the families of glutathione peroxidases (GPxs) and thioredoxin reductases (TrxRs). The family of glutathione peroxidases consists of cytosolic and mitochondria GPx1, gastrointestinal GPx2, plasma GPx3, phospholipid hydroperoxide GPx4, and the olfactory epithe-

lium GPx6. GPx1 is a major antioxidant enzyme *in vivo* and it is irreplaceable by any other selenoproteins (Brigelius-Flohé, Flohé 2016). GPx2 may serve as a first line of defense in exposure to ROS induced by ingested prooixdant or gut microbiota. (Roman et al. 2014). GPx3 is the only extracellular enzyme of GPxs family. It is primarily synthesized in the kidney and from there it is released as glycosylated protein into the extracellular spaces, but the major fraction remains bound to the base membrane of a kidney (Avissar et al. 1994). GPx3 is also expressed by the gastrointestinal tract, lung, liver, heart, brain, breast and adipose tissue (Roman et al. 2014). Moreover, this enzyme is highly expressed in the thyroid gland, where it catalyzes the polymerization of thyroglobulin to the highly cross-linked storage form (Schmutzler et al. 2007). GPx4 specifically prevents lipid peroxidation in cell membranes. The expression of GPx2 and GPx4 is more resistant to dietary Se deficiency in comparison to the expression of GPx1 and GPx3. Another form of glutathione peroxidase is found in high concentrations in spermatozoa, where it is involved in sperm maturation and the prevention of cellular apoptosis (Patrick 2004).

Three isoforms of human thioredoxin reductases (cytosolic TrxR1, mitochondrial TrxR2, and thioredoxin glutathione reductase TrxR3) catalyze the NADPH dependent reduction of thioredoxin and therefore play a regulatory role in its metabolic activity. They provide reducing equivalents to the disulphide bonds in enzymes such as thioredoxin peroxidase, ribonucleotide reductase, in and transcription factors (Rundolf, Arner 2004). Therefore they play important role in the reduction of nucleotides (Mustacich, Powis 2000), regulation of transcription, and sperm maturation, the cell growth and inhibition of apoptosis (Roman et al. 2014). TrxR1 and TrxR2, both appear to be involved in embryogenesis, TrxR2 is involved in control of mitochondrial redox processes by reduction of cytochrome c, and takes part in apoptosis signaling (Nalvarte et al. 2004). Activity of thioredoxin reductase depends on the cellular selenium level.

The second major active class of selenoproteins are the iodothyronine deiodinases (DIOs), the family of three integral membrane enzymes. They take part in the thyroid hormone metabolism by catalyzing the activation (DIO1, DIO2) or inactivation (DIO3) of tetraiodothyroxine (T4), triiodothyronine (T3), and reverse-triiodothyronine (rT3). DIO1 and DIO3 are found in plasma membrane, whereas DIO2 is localized in the endoplasmic reticulum membranes. DIO1 is responsible mainly for the control of circulating triiodothyronine level, whereas DIO2 and DIO3 are involved in the regulation of deiodination processes in the thyroid gland (Baqui et al. 2003). If the thyroid gland functions properly, it has the ability to maintain a high level of selenium in serum even if the dietary intake of this element is insufficient (Szybiński et al. 2010)

Expression of selenoproteins is strictly controlled by the selenocysteine translational process, which is highly dependent on the presence of selenium (Turanov et al. 2011). Selenium deficiency reduces the intracellular amount

of mature tRNA-Sec, which in turn results in decreased selenoproteins synthesis. However, there is a hierarchy of selenoproteins expression. Selenoprotein synthesis is also considered to be modulated by different expression of two selenocysteine tRNA isoforms, which are distinguished by the presence of 2-O-methylribose at position 34 (Um34). The Um34 modification is also dependent on selenium availability. The mutation of the selenocysteine tRNA gene (TRSP) which interferes with the Um34 modification has recently been described in a human organism, where authors noted decreased expression of stress-related selenoproteins (GPx1 and GPx3), while the expression of housekeeping selenoproteins, essential for survival, was largely preserved (Schoenmakers et al. 2016).

Selenoprotein biosynthesis is hierarchically organized, which means that an individual selenoprotein level does not respond identically to the alimentary selenium supply. Additionally, the fact that there is hierarchical demand of tissues for selenium complicates this hierarchy (Sunde 2012, Barret et al. 2016). GPx1 and GPx3 rank low in the hierarchy, GPx4, depending on the tissue, ranks medium to high, and GPx2 ranks the highest. This implies that the hydroperoxide metabolism responds to selenium restriction in a tissue-specific manner depending on the expression pattern of the enzymes involved. TrxR3 ranks higher than TrxR1 and TrxR2. The three deiodinases rank high. Selenium is delivered to particular tissues as selenoprotein-P, whose uptake by lipoprotein receptors differs among tissues. In consequences, a protein like GPx4 ranks so high in the testis that it can hardly be depleted, but will readily decline due to selenium restriction in a non-privileged tissue such as the liver (Sunde 2012).

Approximately 60% of selenium in the plasma is incorporated in selenoprotein-P (SEPP1), which contains 10 Se atoms per molecule as selenocysteine. Selenoprotein-P is expressed in many tissues, suggesting that it plays a central role in selenium supply to tissues and participates in the regulation of selenium metabolism in an organism. However, it is important to note that SEPP1 acts also as an antioxidant enzyme and may serve as a heavy-metal (eg. mercury) chelator (Reeves, Hoffman 2009, Barret et al. 2016). Aside from the normal antioxidant activity contributed by selenocysteine, selenoprotein S (SepHS2 – selenophosphate synthetase 2) and selenoprotein 15 (selenoprotein F, the 15 kDa selenoprotein Sep15) can process and remove misfolded proteins (Labunskyy et al. 2009), while MsrB1 (methionine-R-sulfoxide reductase 1) is capable of regulating antioxidant protein repair through protein disulfide shuffling (Kaya et al. 2015). The role of many human selenoproteins is still unknown or not fully elucidated.

SELENIUM AND HEALTH OUTCOMES

Health effects of deficiency or excess of selenium

Selenium deficiency can result in significant deterioration of health and development of serious illnesses. Recently the German, Austrian and Swiss nutrition societies have revised and published (February 2015) the reference values for the intake of selenium. The saturation of selenoprotein P in the plasma is used as a criterion for the derivation of reference values for selenium intake in adults (Kipp et al. 2015).

It is very hard to establish what dose becomes toxic because toxicity of selenium is dependent on its form present in food, exposure time, physiological status, interaction with other metals as well as specific interactions between metabolites and gene expression mechanisms in the human organism (Fairweather-Tait et al. 2010). The total amount of selenium in a human organism varies from 10 to 20 mg and depends on personal features, diet and geographical location of particular population. The kidneys, testes and liver have the highest concentration of Se. Normal blood concentration of selenium varies from 50 to 340 μg L^{-1}. Toxic effects in humans have been seen at blood levels ranging from 300 to 7500 μg L^{-1}. In most parts of the world, normal urine level is <30 μg L^{-1}. In Poland, the average daily dose of selenium does not exceed 30-40 μg, which is an insufficient dose (Zagrodzki, Łaszczyk 2006).

Selenium toxicity can be attributed to redox cycling, whereby the superoxide anion and ultimately H_2O_2, and other reactive oxygen species (ROS) are generated. This process can trigger programmed cell death, the mechanism which appears to depend on a cell type (Park et al. 2012). Comparison of a large variety of selenium compounds revealed that this kind of selenium toxicity is restricted to compounds with selenium in the oxidation state -2 (i.e. the selenol state) or to those that can be physiologically metabolized to selenol (see Figure 1). Partial or complete regeneration of the selenol state is achieved by thiols. In apoptosis driven by redox cycling of selenium compounds, the oxidant culprits are ROS. Therefore, all kinds of peroxidases, in particular of the GPx family, inhibit oxidant-triggered apoptosis. This implies that enzyme-bound selenium has an opposite effect to redox-cycling of free selenium compounds, which agrees with the observation that selenium deficiency can resemble selenium toxicity in many respects.

Insufficient dietary supplementation of selenium is associated with several health problems. The first documented pathological state is ROS-dependent damage. It is proven that the extent of damage caused by ROS can be alleviated or even eliminated by the administration of organoselenocompounds in diet. Decrease of glutathione peroxidase gene expression due to deficiency of selenium has been associated with a decrease in concentrations of thyroid hormones, known to increase after selenium supplementation (Zagrodzki, Łaszczyk 2006, Köhrle 2015). Glutathione peroxidase was also

proven to affect cholesterol hydroxides or oxysterols levels. Oxysterols manifest apoptotic activity on smooth muscle vessel cells, which is inhibited by selenoproteins (Poirier et al. 2010). Selenium deficiency contributes to various forms of heart disease such as endemic cardiomyopathy, termed the Keshan disease, or the degeneration of organs and tissues manifested as Kashin--Beck disease (Navarro-Alarcon, Cabrera-Vique 2008).

High intake of selenium causes selenosis, which can affect people exposed to selenium intake that reaches 1000 μg per day or more. However, selenium poisoning or selenosis is very rare. Selenium toxicity (endemic chronic selenosis) was reported among Chinese people who ate crops with high Se content. Nail deformation, hair loss and skin rash, lesions of the nervous system, fatigue and irritability were observed (reviewed in ref. Navarro--Alarcon, Cabrera-Vique 2008, Zvolak, Zaporowska 2012). In addition, acute Se poisoning was observed a few years ago in the United States among people who took liquid dietary supplement containing 200-times higher Se content than was labelled (Macfarquhar et al. 2010). Acute selenium toxicity causes severe neuronal lesions, gastrointestinal and respiratory symptoms, kidney failure and cardiac disorders (Navarro-Alarcon, Cabrera-Vique 2008). Exposure to the toxic level of selenium can have a negative impact on genetic integrity, although the International Agency for Research on Cancer (IARC) concluded that there are no sufficient data to consider selenium to be a carcinogen for humans (IARC 1987).

Immunomodulatory effect of selenium

Organoselenium compounds show an immunomodulatory effect, which has been examined recently in studies regarding the effect of selenium on two autoimmune diseases: Grave's hyperthyroidism and Hashimoto's thyroiditis (Watt et al. 2013, Van Zuuren et al. 2014). The concentration of selenium is high in the thyroid gland and three important groups of enzymes within the thyroid are selenoproteins. Most authors claim that selenium affects the immune system through the regulation of the production of reactive oxygen species and their metabolites. Selenium supplementation appears to reinforce intrathyroidal GPx and TrxR activity, probably by increasing the concentration of selenium within the thyroid. The beneficial effects of selenium on thyroid autoimmune parameters appear to be interesting but very few data are available on clinical applications (Drutel et al. 2013).

Selenium may have beneficial effects on autoimmune hypothyroidism and on Graves' orbitopathy. Watt et al. (2013) hypothesize that adjuvant selenium may be beneficial in the treatment of Graves' hyperthyroidism. The authors explored whether selenium supplementation combined with standard treatment with anti-thyroid drugs versus standard treatment with anti-thyroid drugs led to a decline in anti-thyroid drug treatment failure, more rapid and longer lasting remission and improved quality of life in patients with Graves' hyperthyroidism (Watt et al. 2013). Graves' disease, which can

be occasionally associated with thyroid eye disease (TED), needs further studies to determine whether selenium supplementation is beneficial for patients diagnosed with Graves' disease to prevent development of TED (Khong et al. 2014). Research suggests that there is a small but significant difference in selenium levels between Graves' disease patients with TED compared with patients who do not have TED. Recently, Dehina et al. (2016) has published results of studies showing lack of association between a selenium status and the severity of an illness due to Graves' ophtalmopathy.

Selenium supplementation of people with Hashimoto's thyroiditis may reduces anti-TPO antibody levels and result in a decreased dosage of levothyroxine. Van Zuuren et al. (2014) published results of systematic review assessing the effects of selenium supplementation on this thyroiditis. The conclusion was that the evidence to support or refute the efficacy of selenium supplementation of people with Hashimoto's thyroiditis is incomplete and not reliable to help informed clinical decision making (Van Zuuren et al. 2014).

Selenium and inflammation

Selenium is involved in a decrease of prostaglandins, prostacyclins, thromboxanes, and the leukotrienes synthesis from arachidonic acid released from membrane phospholipids by phospholipase A_2 (Kaushal et al. 2012). Glutathione peroxidases keep all kinds of lipoxygenases and cyclooxygenases in a dormant status. GPx1 has been shown to inhibit leukotrienes biosynthesis in human monocytes (Straif et al. 2000). In the intestine, it is primarily GPx2, which inhibits inflammation by downregulation of cyclooxygenase 2 (COX2) (reviewed in ref. Brigelius-Flohé, Kipp 2012). However, silencing lipoxygenases by Gpx may also prolong their life time and, thus, the duration of an inflammatory response, since all lipoxygenases tend to be irreversibly inactivated by excess of their own products. GPx1 and GPx4 also decrease inflammatory response by inhibiting TLR4- or TNFα-mediated activation of NF-κB (Maehira et al. 2003). Because patients with inflammatory bowel disease demonstrate nutritional deficiencies and are at increased risk for colon cancer due to heightened inflammation and oxidative stress, dysfunction of selenoproteins may contribute to disease progression. Over the years, numerous studies have analyzed the effects of selenoprotein loss and shown that they are important mediators of intestinal inflammation and carcinogenesis. Recently, Barrett et al. (2016) has focused on the role of selenoprotein P, a major selenium transport protein, which also has an endogenous antioxidant function. These authors showed that SEPP1 loss altered immune and epithelial cellular function in a murine model of colitis-associated carcinoma.

Selenium and cancer

Certain selenoproteins provide a tool to regulate hydroperoxide-mediated signalling. Three selenoproteins have been particularly instructive for under-

standing the role of selenoproteins in cancer. These proteins, TrxR1, Sep15, and GPx2, were found to exhibit a split "Dr Jekyll and Mr. Hyde" faces, both preventing and promoting cancer (Brigelius-Flohé, Kipp 2012, Yoo et al. 2012). TrxR1 is over-expressed in breast cancer (Turunen et al. 2004), colorectal cancer (Raffel et al. 2003), hepatocellular carcinoma (Kawahara et al. 1996) and gastric carcinoma (Grogan et al. 2000). Mammalian gastrointestinal GPx2, which ranks high in the hierarchy of selenoproteins, plays the role in tumorigenesis. Colocalization of GPx2 with the Wnt pathway in crypt bases of the intestine and its induction by Wnt signals point to a role in mucosal homeostasis, but GPx2 might also support tumor growth when increased by a dysregulated Wnt pathway. In contrast, the induction of GPx2 by Nrf2 activators and the upregulation of COX2 in cells with a GPx2 knockdown reveal inhibition of inflammation and suggest prevention of inflammation-mediated carcinogenesis. The Janus-faced role of GPx2 has been confirmed in a mouse model of inflammation-associated colon carcinogenesis, where GPx2 deletion increased inflammation and consequently tumor development, but decreased tumor size. The model further revealed GPx2-independent decrease in tumor development by selenium and detrimental effects of the Nrf2-activator sulforaphane in moderate Se deficiency (Brigelius-Flohé, Kipp 2012). Selenium deficiency is known to increase cancer risk by so far unclear mechanisms. Selenium deficiency does not only reduce synthesis of selenoproteins but also affects the expression of other proteins and, thus, affects pathways. A moderate Se deficiency activates the Nrf2 and the Wnt pathways. The link between both pathways appears to be GSK3ß (glycogen synthase kinase 3 B), which in the active state prepares Nrf2 as well as ß-catenin, the key player in Wnt signalling, for ubiquitination and proteasomal degradation, thus silencing their transcriptional activity. Upon stimulation by Wnt signals, GSK3ß becomes inactivated and transcription factors are stabilized. Many intermediate steps in both pathways can be modulated by hydroperoxides, making them predestined to be regulated by selenoproteins. The Keap1/Nrf2 system is generally believed to protect against oxidative stress, xenobiotics, inflammation and carcinogenesis, while the Wnt response is considered rather a risky one in these respects. However, not only healthy cells but also malignant cells benefit from intact Keap1/Nrf2 signalling, making a dysregulated hydroperoxide signalling a plausible explanation for the increased cancer risk in selenium deficiency (Brigelius-Flohé, Kipp 2013).

There is growing evidence regarding the anticancer activity of organoselenium compounds. Anticancerogenic activities have been demonstrated for selenodiglutathione, hydrogen selenide, methylated metabolites of selenide, selenomethionine and methylselenol. These metabolites execute several functions of Se-anticarcinogenesis at (i) underlying levels (redox cycling, modification of protein-thiols, methionine mimicry) and (ii) intermediate levels (DNA damage and repair) (Jackson, Combs 2012). Irons et al. (2006) described that Se in the form of both low molecular weight compounds and seleno-

proteins reduced colon cancer risk in transgenic mice. Methylselenol, a metabolite of selenobetaine or Se-methylselenocysteine, is also thought to have anticancer effect. It kills transformed cells through mechanisms that include increased formation of ROS, induction of DNA damage, triggering of apoptosis and inhibition of angiogenesis (Hagemann-Jensen et al. 2014). The most promising results of studies on selenium supplementation were obtained in prostate cancer research. This particular cancer type represents high susceptibility to selenium. Studies regarding the use of organoselenium compounds in prostate cancer treatment showed a decrease of cancer development (Zhao et al. 2006). The chemo-preventive role of selenium appears to be related to its anti-inflammatory action outlined above.

SUPPLEMENTS AS AN ALTERNATIVE SOURCE OF SELENIUM

Apart from dietary sources of selenium, people can consume this element in the form of supplements, which allows them to control doses and avoid selenium poisoning. At present, there is a wide range of dietary supplements containing inorganic and organic Se-compounds. There are two types of nutritional supplements based on selenium: (i) multi-vitamin and multi-mineral preparations containing inorganic selenium, other trace elements and vitamins, and (ii) supplements based on Se-enriched *Saccharomyces cerevisiae* yeasts (Se-yeasts) (Navarro-Alarcon, Cabrera-Vique 2008). The first batches of Se-yeasts became available in the early 1970s. It has the ability to assimilate up 3000 μg g^{-1} of Se starting from sodium selenite added to the growth medium (Roman et al. 2014). High-quality Se-yeasts do not differ in respect to taste, appearance and smell from traditional yeasts. The use of such yeasts as an additive to food has a number of advantages compared with undiluted selenium compounds. Se-yeasts are stable on storage and safeguarded against dosage errors that can occur when undiluted selenium compounds are directly added to food. The SeMet from yeast proteins represents a slow -release form of selenium, eliminating the possibility of a sudden increase in the levels of selenium after consumption (Schrauzer, Surai 2009). Because Se in Se-yeasts is stable even at higher temperature, it can be used instead of conventional yeast for baking bread (Dumont et al. 2006). Additionally, *S. cerevisiae* have a high protein content, which improves Se absorption. SeMet is also the main selenium compound detected in the fruit bodies of *Agaricus bisporus* and *Lentinula edodes* (Shiitake), one of the most popular edible mushrooms in the world, when is cultivated on a medium supplemented with selenium (Turło et al. 2010).

CONCLUSIONS

Selenium, which was discovered in the 19th century, is an essential nutritional element in a human diet. It can be administrated in both organic and inorganic forms, although organic forms are easier to be ingested than inorganic ones. The biological functions of selenium are largely mediated by selenoproteins. Human selenoproteins encoded by 25 genes are involved in glutathione-dependent hydroperoxide removal, reduction of thioredoxins, selenophosphate synthesis, activation and inactivation of thyroid hormones, repair of oxidized methionine residues and ER-associated protein degradation. These functions are responsible for the role of selenium in human health, including its pro- and anticancer activities, roles in the immune system and other functions. There are many aspects of the metabolism of selenium and selenoproteins that remain to be investigated, and there are still many unresolved questions, e.g. What are the biological roles of the approximately one-half of the human selenoproteins which functions are unknown? Can dietary selenium have protective effect not only as a component of selenoproteins? What is the contribution of dietary selenium to healthy ageing and how does selenoprotein expression affect diseases like diabetes, different cancers, cardiovascular or neurological disorders? Furthermore, despite intensive evaluation of the beneficial and detrimental effects of selenium in human clinical trials, we still do not exactly know how selenium and selenoproteins act to prevent and, in some cases, promote cancer. Explanation of these basic processes will lead to new strategies for therapeutic intervention.

DECLARATION OF INTEREST

The authors declare no conflict of interests.

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