Pharmacological properties of selenium and its preparations: From antioxidant to neuroprotector

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Review Article

Pharmacological properties of selenium and its preparations: from antioxidant to neuroprotector

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Abstract

Selenium is an essential component of more than two dozen enzymes and other selenoproteins that play critical roles in reproduction, DNA synthesis, thyroid hormone metabolism, and protection from oxidative damage and infection. Selenium has a protective action against some forms of cancer and cardiovascular diseases, modulates levels of inflammatory mediators, promotes to maintain bone homeostasis and protects against bone loss. Selenium significance as a cardioprotective agent may be associated not only with its antioxidant properties, but also with its ability to prevent inflammation, autophagy, as well as the intrinsic and extrinsic apoptosis pathways. Signaling pathways, such as p-AMPK, PARP, Nrf2, STAT, are involved in the protective effects of selenium. Selenium protects against cardiovascular damage by increasing the survival rate of cardiomyocytes, including a mitochondria-dependent pathway and autophagy through peroxisome proliferator-activated receptors. Research demonstrating neuroprotective and cardioprotective effects of selenium preparations – selenoline, selenocysteine and selenomethionine – is growing at a rapid rate. It has been established that these compounds are able to normalize the levels of heat shock proteins (HSP70), which limit the cytotoxic effects of free radicals, produce energotropic action, prevent a decrease in the membrane mitochondria charge, and the opening of the mitochondrial pore. Also regulate the expression of transmembrane factors NF-kB, c-fos, which is associated with their main biological function of chaperone proteins, providing protection of neurons from damage. In this review, we want to emphasize pharmacological role of Selenium and its derivatives on human health is very complex and has yet to be fully understood.

Keywords

selenium, heat shock proteins, cardioprotective, neuroprotective, antioxidant action.

Introduction

Selenium, the 34th element of the periodic table placed in the subgroup VIA (also called chalcogen group), is the electronic and chemical analogue of sulfur, a multifunctional (e.g. antioxidant, antineoplastic, antidiabetic, antimicrobial) nutrient element. Selenium is one of the most important trace elements in the human body, nutritionally essential as a component of more than two dozen enzymes and other selenoproteins that play critical roles in

reproduction, DNA synthesis, thyroid hormone metabolism, and protection from oxidative damage and infection (Rakov and Muz 2019). The human body absorbs more than 90% of selenium from plant and animal food, and about 10% – with drinking water (Krelszek et al. 2021). Dietary selenium deficiency can lead to the development of severe and dangerous diseases, such as cardiomyopathy, arrhythmias, and increased susceptibility to infection (Yovanovich and Ermakov 2020). Conversely, a selenium-excessive diet can cause acute poisoning and chronic symptoms. Classical symptoms of dietary selenium deficiency in farm and laboratory animals were characterized in the 1950s to 1960s, and selenium supranutrition was found to have anti-cancer properties without affecting healthy cells and cancer mortality in the 1990s (Alhasan et al 2019). Its anti-cancer properties are related to antioxidant and prooxidant activity. Selenium-loaded bone frameworks have potential for cancer treatment and regeneration. Many studies report that selenium has a protective effect against some forms of cancer, cardiovascular disease mortality, regulates the inflammatory mediators in asthma, maintains bone homeostasis and protects against bone loss. Antioxidant properties of selenium preparations have been widely studied and discussed in a number of recent review articles (Rahmanto and Davies 2012; Steinbrenner and Sils 2013; Solovyev 2015; Gandin et al. 2018; Talbi et al. 2019; Chen et al 2020; Kuria et al. 2020; Wang et al. 2020). Selenium is widely used in industry for the manufacture of several products, such as semiconductors, photovoltaic cells (due to its ability to convert light energy into electrical energy), rectifiers, corrosion-resistant alloys, pigments (red and orange color) for paints, ceramics, glass-making process and pharmaceutical substances for the creation of mono-drugs and complex drugs, which have a wide spectrum of action (Rahmanto and Davies 2012).

Selenium was discovered in 1817 by the Swedish chemist J.J. Berzelius, who named the new element from the Greek word 'Selene', meaning Goddess of the Moon (Duntas and Benvenga 2015). In terms of chemical properties, it is similar to tellurium, discovered in 1782 by M.H. Klaproth (Rakov and Muz 2019). The history of the study of the biological role of selenium includes 3 periods. Selenium was considered highly toxic to the body until 1857 (Golubkina et al. 2017). The reason for this statement was the massive poisoning of livestock in some areas of the Great Plains in the United States. The next stage, characterized by the emergence of interest in selenium, was the discovery by K. Schwartz and S. Foltz in 1857 that established the prevention of developing liver cirrhosis in rats and exudative diathesis in chickens by sodium selenite administered in very low doses. This was the beginning of the use of selenium for the treatment of white muscle disease and other diseases in animals. The third stage started with the discovery of the selenium-containing enzyme, glutathione peroxidase, regulating the antioxidant state of the body and also contributing to the identification of the areas where the lack of selenium in the environment and food products were established (Golubkina et al. 2017). However, it was not until 1873 when all the aspects of the biochemical mechanisms of action of selenium on organs and tissues were disclosed. In 1873, J. Rotrak with co-authors and a group of German scientists led by L. Flos (Yovanovich and Ermakov 2020) demonstrated the effect of selenium on the metabolic parameters of living organisms. Selenium supports the function of several systems, including the endocrine, immune, and cardiovascular systems. The thyroid is the organ with the highest concentration of selenium per weight of organ tissue. About 25 proteins were discovered to contain a selenocysteine in place of the more common sulfurated amino acid. In these proteins, selenocysteine, present in the active site of the enzyme, is essential for its catalytic activity. Selenium acts in the catalytic center playing a principal role in several major metabolic pathways, such as thyroid hormone metabolism, immune functions, and antioxidant defense systems.

Nowadays, much evidence demonstrated the role of glutathione peroxidase, and that this enzyme, like catalase, with its antioxidant properties, protects erythrocyte membranes from oxidation by destroying hydrogen peroxide. This work (Wichman et al. 2016) became a trigger for the discovery of other selenium-containing enzymes, such as 3 types of oxidoreductases – iodothyronine deiodinases (D1, D2, D3), which catalyze the activation and inactivation of thyroxine with the formation of active triiodothyronine and reverse triiodothyronine in deiodination reactions.

Deiodinases have tissue and organ specificity, which is determined by their different localization. D1 is predominantly expressed in the liver, kidneys, thyroid gland and pituitary glands; D2 – in the gastrointestinal tract, heart, central nervous system, pituitary gland, skeletal muscle, brown adipose tissue, and placenta; D3 – in the in pregnant uterus and placenta, in the liver, brain, and skin of the embryo.

The important role of selenium and its derivatives

Selenium and its derivatives have pronounced antioxidant properties, even if they are a part of complex compounds. Feeding healthy rats with chlorella algae, which contains a significant amount of selenium, has lowered the levels of lipid peroxidation indicators in the organs and plasma of animals, such as malondialdehyde and diene conjugates, while increasing the levels of indicators of antioxidant protection, such as the activity of superoxide dismutase, succinate dehydrogenase, catalase, and cytochrome-C-oxidase (Krelszek et al. 2021).

Selenoproteins, due to their enzymatic role, have antioxidant properties that are more marked inside cells. It is selenoproteins that play a decisive role in maintaining the levels of selenium in the body and preventing organ

dysfunctions associated with changes in homeostasis. Selenocysteine and selenomethionine are key forms of selenoproteins and are found in various tissues of the body. Selenocysteine is found in animal tissues, while selenomethionine is obtained from yeast, algae, and some plants (Krelszek et al. 2021).

Selenoprotein P, a selenium-rich plasma protein, is a glycoprotein that plays an important role in selenium metabolism. Decreased selenoprotein P expression is associated with dietary selenium deficiency. The fall in selenoprotein P concentration in plasma is associated with dietary selenium deficiency, as a result of which oxidative stress may develop. Selenium administration first leads to an increase in the levels of selenoprotein P, and then of other proteins. Selenoprotein P is mainly produced in hepatocytes, although it is found in plasma and other tissues (Steinbrenner and Sils 2013). Selenoprotein P consists of two domains: the larger N-terminal domain responsible for maintaining the redox potential in the cell, and the smaller C-terminal domain, which provides selenium transport.

Selenoprotein P is expressed in testes, brain tissues, and liver. It is considered a marker of selenium in the body. Selenoprotein P maintains homeostasis, protects lipoproteins from oxidation by removing the peroxynitrite molecule, which is formed due to oxidative stress inside the cells as a result of the reaction between superoxide ions and nitric oxide molecules at the sites of inflammation (Di Giuseppe et al. 2019). Selenoprotein P enters the circulatory system and is a source of selenium for peripheral tissues (Talbi et al. 2019). With a sufficient intake of selenium with food, its content increases more significantly in the nervous system and testes, while the levels of selenium increase insignificantly in the kidneys and other organs. It should be noted that recent advances in the selenium field have not only contributed to our better understanding of how selenium functions at the molecular level, but also provided complicated details on general protein translation mechanisms and evolution of the genetic code.

Selenoprotein W, a small size of 9 kDa, one of the most widespread selenoproteins found in the cytosol, is detected in high concentrations in muscles and the brain. It is essential for muscle metabolism, and skeletal muscle calcification. Selenium supplements are prescribed prophylactically in cattle and sheep for enzootic muscular dystrophy, commonly known as white muscle disease (Yildirim et al. 2019). Besides, the level of selenoprotein W deficiency may be correlated with the occurrence of stress, since the severity of stress is strongly influenced by the bioavailability of selenium.

All thioredoxin D1, D2, D3 enzymes act as intracellular antioxidant molecules, regulating redox reactions; therefore they are the main factors of apoptosis and DNA synthesis. It is believed that thioredoxin acts as a key enzyme in selenium metabolism, providing the synthesis of selenoproteins (Weekley and Harris 2013). Thioredoxin activates the p53 tumor suppressor gene, so D1 is strongly expressed in all carcinoma cells. In addition, inhibition of thioredoxin D1 enzyme in cancer cell lines contributes to a decrease in cell proliferation and cancer progression by administering knockdown D1 cells to mice. D1 may have two opposite functions in the development and progression of cancer. On the one hand, D1 can help prevent cancer by maintaining the redox balance of cells and reducing the frequency of mutations that cause tumor development. On the other hand, D1 is also important for tumor progression because cancer cells are very susceptible to oxidative damage (Kieliszek et al. 2019).

Glutathione peroxidase performs several functions in the body, regulating detoxification processes and redox homeostasis (Jiao et al. 2017). Glutathione peroxidase is expressed in the erythrocytes, plasma, extracellular fluid, kidneys, lungs, liver, thyroid gland, heart, testes, and placenta (Liu et al. 2021). Glutathione peroxidase is detected in mitochondria, cytosol, and nucleus (Alhasan et al. 2019). The enzyme is essential for the maturation of sperm motility and effectively improves male fertility (Alhasan et al. 2019).

The number of reports that trace the relationship between pathogenesis of some diseases and prolonged dietary selenium deficiency or selenium excess is growing annually (Hadrup and Ravn-Haren 2020), and it is proposed to use new selenium preparations and other selenium-containing sources, such as algae (Viniarska et al. 2017).

Organoselenium compounds behaving very similarly to their organosulfur analogs have been synthesized in recent years; however, selenium single bondcarbon bonds are typically weaker. The selenium functionality to see broad application in organic synthesis is the selenide, analogous to the sulfide. The attention was paid again to ebselen, and then diselenides appeared, which are united by similar antioxidant and anti-inflammatory properties. It is assumed that these properties are realized due to the activation of transcription factors that regulate the expression of antioxidant genes (Nogueira et al. 2021).

Thiol-containing compounds can be lithium mimetics and used as protease inhibitors in SAPS-COV-2 (Heller et al. 2020). Selenium has been compared to vitamin E as a protector of cell membranes from oxidation. Vitamin E directly absorbs phospholipid hydroperoxide radicals, while selenium in hydroxy peroxidase reduces the levels of phospholipid peroxides, which can generate reactive peroxide radicals (Chen et al 2020).

Selenium is widespread not only in the biosphere, but also in the atmosphere. Hydrogen selenide, dimethyl selenide, and selenium oxide are determined in the atmosphere (Hossain et al 2020). Selenium can be found in plants in the inorganic form, such as selenites, selenates, elemental selenium and others. In plants, these forms are converted into organic compounds, mainly selenocysteine and selenomethionine. In human and plant biological systems, selenomethionine replaces methionine. Among plants that accumulate selenium are lucerne, cruciferous species, such as cabbage, broccoli and cauliflower,

as well as yeasts. Most selenium in animal tissue in the form of selenomethionine is primarily stored in the skeletal muscle that stores anywhere from 28% to 46% of the body's selenium. Seafood and organ meats are noted as the sources that contain the highest levels of selenium, while other good products include muscle meats, cereals, and dairy products (Wichman et al. 2016).

A significant proportion of selenium is contained in the thyroid gland in the form of deiodinases; therefore, hypothyroidism and goiter are common in areas with soil low in selenium (Skowronska-Joozwtak 2015). In autoimmune thyroiditis, selenium reduces the titer of antibodies to thyroid peroxidase and thyroglobulin (Wichman et al. 2016).

Selenium also improves the visual function in patients with endocrine ophthalmopathy, although glucocorticoids have been used to manage severe ophthalmopathy (Bartalena et al. 2016). The anti-inflammatory effect of selenium was first discovered in diabetic rats (Tong et al. 2020). It was shown that selenium can influence inflammatory reactions inducing inhibition of NF-kB, which promotes the production of tumor necrosis factor and interleukins (Lv et al. 2020).

Selenium influences the process of gene transcription responsible for the synthesis of immunoglobulins, which play an important role in the regulation of the activity of the immune system. Selenium levels also determine macrophage differentiation.

More pro-inflammatory macrophages M1 are produced under conditions of selenium deficiency, whereas anti-inflammatory macrophages M2 are mainly formed under conditions of selenium excess.

This model of selenium action makes it possible to induce a proinflammatory cellular immune response against viral and bacterial pathogens using Th1 lymphocytes (Tinggi 2014). The release of inflammatory mediators in the body can trigger the occurrence of various painful conditions, whereas a decrease in selenoprotein activity may be associated with a disruption in the functioning of the antiradical system of the body.

Levels of proteins containing selenocysteine are regulated by markers of inflammation and extracellular sugar levels in liver cells. Selenium-containing proteins have antitumor action in systemic macrophages and brain astrocytes, reducing stress. The protective and antitumor effect of selenium is associated not only with its antioxidant properties, but also with the effect on the immune system, since lipid peroxidation activation reduces the potential of immune reactivity.

Selenium may play a role in the regulation of the redox states of proteins, such as NF-kB transcription factors. Transcription factors regulated by redox mechanisms can have two states, active and inactive, which differ in the oxidation state of the cysteine residue. This is due to the presence or absence of an intramolecular disulfide bond between two cysteine residues. Disulfide formation by oxidation is reversed by cellular systems of disulfide-reducing enzymes, such as glutaredoxin and thioredoxin. Se-derivatives react with protein thiols or disulfides and form more reactive intermediates. In this mechanism, Se acts as a redox catalyst that binds the redox equilibrium of the cell. Se reacts with the cysteine of the non-catalytic thioredoxin site to form the selenenyl sulfide derivative. Modulation of the transcription factor NF-kB by Se can be related to gene expression and regulate the synthesis of enzymes (antioxidants, participants in energy metabolism, glutathione synthesis). An important link in the neuroprotective action of selenium derivatives is the ac-

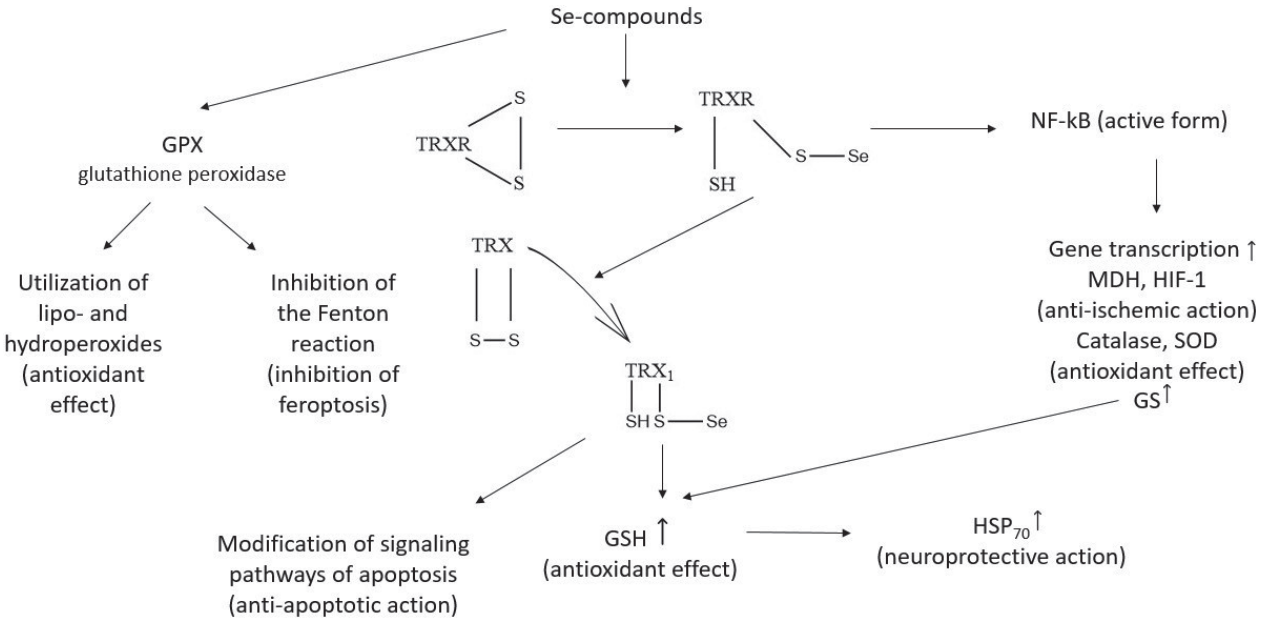

Figure 1. Hypothetical mechanism of action of selenium derivatives. **Note:** TRX – thioredoxin; TRXR – thioredoxin reductase; MGH – malate dehydrogenase; SOD – superoxide dismutase; GS – glutamine synthetase; GPX – glutathione peroxidase; NFkB – nuclear transcription factor; HSP70 – heat shock protein 70 kDa; HIF – hypoxia-induced factor.

tivation of GSH-dependent mechanisms of endogenous neuroprotection, realized by increasing the expression of HSP70 (Fig. 1).

Selenium is necessary for the functioning of the immune system, both the humoral innate and cellular adaptive immune subtypes: it stimulates the function of natural killer cells, increases the production of interleukin-1, interleukin-2, suppresses hypersensitivity of the immediate and delayed types, modulates the phagocytic function of polymorphonuclear leukocytes, antibody response, has antiapoptogenic and radioprotective effects (Saburov et al. 2016).

Selenium preparations exhibit the protective effect on brain tissue, liver tissue, the cardiovascular, endocrine, and reproductive systems. In brain tissue, selenium not only exhibits antioxidant properties, but also takes part in signal transmission in neurons, which helps to maintain cognitive function and prevents the development of Alzheimer's disease (Pillai et al. 2014; Solovyev 2015; Solovyev et al. 2018). Alzheimer's disease is the most common type of dementia with subsequent development of progressive loss of memory, self-expression, face and object recognition, as well as sudden or dramatic changes in behavior.

The levels of selenium-containing compounds affects the levels of mediators, the metabolic activity of neurotransmitters and their structure. That is, impairment of neurotransmitters plays a role in the pathogenesis of the disease on the one hand, and impairment of prooxidant-antioxidant homeostasis, on the other (Loef et al. 2011). The hereditary factors of Alzheimer's disease include the presence of risk factors, the interaction between selenium, apolipoprotein E and presenilin 2.

At the same time, no correlation has been found between the activity of glutathione peroxidase in the cerebrospinal fluid and the occurrence of cerebrolvascular diseases. Changes in calcium metabolism have also been implicated in the pathogenesis of Alzheimer's disease. A decrease in selenoproteins levels can lead to a rapid increase in cytosolic free calcium concentration. The data obtained open up the prospect of using selenium preparations in treating Alzheimer's disease (Reddy et al. 2017; Reeves et al. 2019; Tamtaji et al. 2019; De Silva Leme 2020).

Selenium levels in the body

Insufficient content of selenium, zinc, magnesium, and disturbance of the ratio between them leads to depression (Wang et al. 2018). This is primarily due to the fact that selenium is involved in the antioxidant defense of brain tissue and the nervous system. The daily dose of selenium is 55 mg/kg; it is possible that the serum selenium content is 70–90 mg/L. Such a daily intake of selenium is advertised for the treatment of depression, given that selenium deficiency is noted in pregnancy and kidney diseases when it is used in a milk dose.

The recommended daily intake of selenium is 55 mcg / day, is 55 mg/kg, the content of selenium in the blood serum may be 70–90 mg/L. Such a daily intake of selenium is recommended for the management of depression, taking into account that selenium deficiency is noted in pregnancy and kidney disease when it should be administered in a double dose (Bleys et al 2009). Selenium deficiency was established during the use of neuromodulators and a decrease in the levels of brain-derived neurotrophic factor (Iglesias et al. 2013). Beyond mood and general well-being, the role of selenium on mental health is complex and has yet to be fully understood (Conner et al. 2014), and research linking the two is growing at a rapid rate. In recent years, evidence has shown that a drop in blood selenium levels correlates with the development of mental health conditions, including depression and anxiety disorders (Miyniec et al. 2015).

The administration of selenium compound m-trifluoromethyl-diphenyl-diselenide to rats relieved depressive symptoms (Bruning et al 2011), and vice versa, a decrease in the selenium content in the diet of women increased the risk of depression (Pasco et al. 2012).

At the same time, it was noted that depression had not disappeared after the intake of sufficient selenium doses in geriatric patients (Gao et al. 2012), as well as during hemodialysis (Ekramzadeh et al. 2015). It should be noticed that depression may develop even during selenium intake, when its blood levels exceeded 82–83 mg/L (Colangelo et al. 2014).

The mechanism of the antidepressant effect of selenium is associated with its influence on the dopaminergic and serotonergic systems, possibly with blockade of MAO activity, and increased sensitivity of 5-HT receptors (Bruning et al. 2009; Solovyev 2015). It is considered that selenium due to its antioxidant effect can be recommended for the management of cardiovascular diseases and hyperlipidemia (Gharipour et al. 2017).

A decrease in selenium intake in some countries correlated with an increased risk of cardiomyopathies and cardiovascular diseases in general (Jenkins et al. 2020; Kuria et al. 2020).

Studies investigating the role of selenium deficiency in the development of cardiovascular diseases have shown that a correlation between insufficient selenium intake and the development of cardiovascular diseases may result from the presence of oxidative stress, as well as its complications (Al-Mubarak et al 2020; Gac et al. 2020).

Animal experiments carried out on animals with the decreased activity of glutathione peroxidase have shown that the restoration of glutathione peroxidase activity after the administration of selenium compounds occurs with a decrease in the content of active oxygen radicals. Selenium deficiency decreases the number of receptors for low density lipoprotein, which are necessary for cholesterol level regulation (Toppo et al. 2009; Talbi et al. 2019; Tong et al. 2020).

It should be noted that the number of low density lipoprotein receptors, which are necessary for the regulation

of cholesterol levels, decreases with selenium deficiency. A drop in selenium levels is associated with the risk of coronary heart disease when oxidative stress develops (Joseph and Weber 2013).

Selenium is also involved in the synthesis of an important cardioprotective agent coenzyme Q, a powerful antioxidant (Rees et al. 2013). In addition, selenium has hypolipidemic effects, especially when combined with tocopherol (Jin et al. 2011).

After the combination of selenium with amino acids, selenocysteine, selenomethionine, methylselenocysteine, and selenocystathionine are formed, which have organoprotective effects and play an important role in enzymatic reactions. Selenocysteine is present in the active site of glutathione peroxidase, which reduces the levels of hydrogen peroxide and organic peroxides. These compounds can regulate apoptosis, proliferation, and reproductive processes (Mehdi et al. 2013; Gac et al. 2020).

The development of cardiomyopathies, Keshan disease, and heart failure are associated with selenium deficiency in humans. In the first place, the levels of selenoproteins and, what is especially important, the activity of glutathione peroxidase, and succinate dehydrogenase are significantly reduced in such patients (Van der Pol et al. 2019; Bomer et al. 2020; Al-Mubarak et al 2021). Recent studies have shown that selenium significance as a protective agent in heart failure is associated not only with its antioxidant properties, but also with its ability to prevent inflammation, autophagy, as well as the intrinsic and extrinsic apoptosis pathways (Mirdamadi et al. 2019; Al-Mubarak et al 2020; Belenichev et al. 2020). Signaling pathways, such as p-AMPK, PARP, Nrf2, STAT, are involved in the protective effects of selenium (Zhang et al. 2019; Rayman 2020; Shalihat et al. 2021).

In addition, selenium protects against cardiovascular damage by increasing the survival rate of cardiomyocytes, including a mitochondria-dependent pathway and autophagy through peroxisome proliferator-activated receptor (PPAR) (Ren et al. 2016; Wang et al. 2020). It is established that the occurrence of oxidative and nitrosative stress plays a crucial pathophysiological role in the development of cardiovascular and nervous system disorders. One of the main groups of drugs that prevent stress development is selenium preparations. Sodium selenite (selenase, seleno-line) is one of the registered selenium medicines.

The content of components of the enzymatic and non-enzymatic links of the thiol-disulfide system changes in acute disturbance of cerebral circulation. Disturbance of the non-enzymatic link is manifested by a decrease in the content of reduced glutathione, and an increase in oxidized glutathione. At the same time, the levels of cysteine and methionine also fall, against the background of an increase in homocysteine and nitrotyrosine.

It has been shown that cysteine selenite increases the levels of reduced glutathione, cysteine, methionine, and reduces the content of homocysteine and tyrosine to a greater extent than methionine selenite and sodium selenite, Similar alterations in the indices of the non-enzymatic link of the thiol-disulfide system were noted in the myocardium after administration of selenium compounds.

The data obtained indicate the presence of neuro-and cardioprotective activity in compounds of selenium with amino acids (Gorchakova et al 2017). A decrease in the activity of glutathione peroxidase, glutathione reductase, glutathione-S-transferase has been observed in brain tissue of rats under conditions of acute insufficiency of cerebral circulation.

Preliminary administration of selenium preparations may prevent the alterations in the parameters of the enzymatic link of the thiol-disulfide system (Notsek et al. 2015).

Neuroprotective and cardioprotective action of selenium preparations have also been established in relation to their action on heat shock proteins (HSP70). It was also noted that only 40% of rats with neurological disturbances survived on the 4th day after bilateral ligation of the common carotid arteries. The levels of heat shock proteins, which have a regulatory effect on the processes of cell death, decreased in the homogenate of brain tissue (Belenichev 2020).

Introduction of selenium preparations – selenoline, selenocysteine or selenomethionine – for 4 days significantly relieved acute neurological symptoms. Selenoline reduced animal mortality on the 4th day by 30%, methionine selenite – by 35%, and cysteine selenite – by 45%. Course administration of selenium preparations led to the expression of mRNA, to a greater extent with the introduction of cysteine selenite (Belenichev 2020).

The neuroprotective properties of selenium preparations are realized due to their ability to normalize the levels of heat shock proteins that limit the cytotoxic effects of free radicals, produce energotropic action, prevent a decrease in the membrane mitochondria charge, and the opening of the mitochondrial pore, as well as regulate the expression of transmembrane factors NF-kB, c-fos, which is associated with their main biological function of chaperone proteins and providing protection of neurons from damage.

Cysteine selenite demonstrated the most significant impact due to its ability to positively influence on the synthesis of glutathione, modulate expression of selenium glutathione peroxidase, as well as influence on GSH-dependent mechanisms of neuroprotection (Belenichev et al. 2020)

The available literature data indicate that selenium is involved in hepatoprotective mechanisms. A decrease in the levels of blood selenium was noted due to decreased levels of transport selenoprotein P. When modeling liver lesions by the administration of lipoproteins, a disturbance of amino acid transport and production of cysteine selenite have been noted. Therefore, selenium may serve as a marker of liver diseases (Kozeniecki et al. 2020; Sherlock et al. 2020; Gul-Klein et al. 2021).

Selenium is involved in the body's metabolism in several ways. It can be involved in protein synthesis as selenomethionine instead of methionine (easily acylates met-tRNA). Also, through the mechanism of trans-sulfonation, it is converted to selenocysteine, which, through

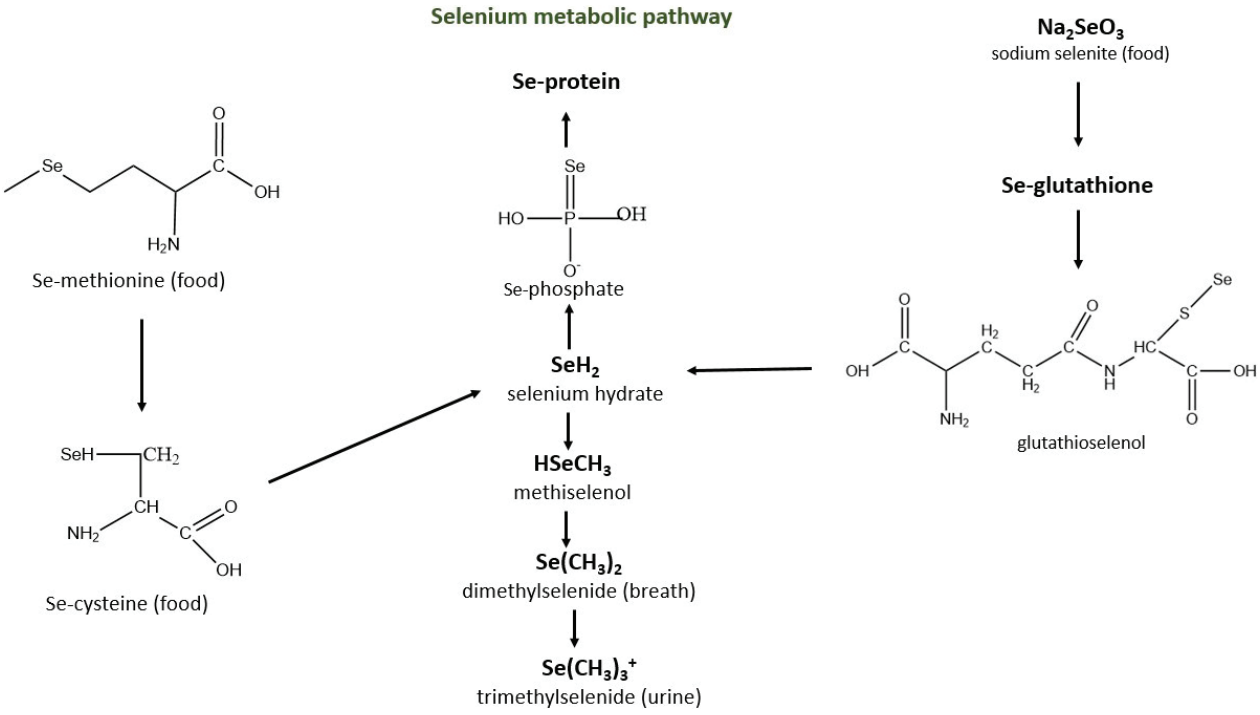

Figure 2. Selenium metabolism in the body.

the stage of formation of selenium hydride, is converted into hydrogen. In addition, selenite is metabolized to hydrogen selenide via selenodiglutathione and glutathione selenopersulfide. Hydrogen selenide is an important donor of active selenium for the synthesis of selenoproteins. The end products of selenium metabolism are dimethyl selenide (excreted by the lungs with exhaled air) and trimethylsnenonium (excreted in the urine) (Fig. 2).

The hepatoprotective effects of selenium preparations along with their cardio- and neuroprotective action were confirmed in the experiments on rats with dichloroethane-induced hepatotoxicity and apoptosis (Pogotova et al 2014). The preventive effect of selenium in diabetes mellitus was also noted. People with higher selenium content in their fingernails have a lower risk of diabetes mellitus development (Rayman et al 2013).

It has been experimentally proven (Fontenelle et al. 2018) that selenium plays a key role in the regulation of glucose homeostasis. Selenium has also been shown to delay the development and progression of type 2 diabetes mellitus. Selenium has been also reported to act as a synergist for insulin (Piagmentini et al. 2017; Fontenelle et al. 2018; Wang et al 2020). With an increase in plasma selenium concentration above 140 ng/ml, the risk of type 2 diabetes mellitus development increases (Hofstee et al. 2020).

Selenoproteins are important active physiological antioxidants capable of exhibiting insulin-like properties that can interfere with insulin signaling (Kohler et al. 2018).

The reaction of beta cells of the pancreas to the administration of selenium is known, indicating both high bioavailability of selenium and its synergism with insulin (Kim et al. 2019). Selenium affects the reproductive organs in both men and women (Saitar 2021), and is essential for the processes of fertilization and reproduction in men and women. At the same time, even low selenium levels can increase spermatozoa susceptibility to free radicals, which can disrupt biochemical processes in the acrosome (Stoedter et al. 2010).

A decrease in selenium levels reduces spermatozoa motility and causes morphological changes in the head of the penis (Ahsan et al. 2014). The effect of selenium on spermatozoa motility is especially beneficial when combined with vitamins A, C, and E (Mintziori et al. 2020). Improving sperm motility takes place along with an increase in glutathione peroxidase activity. Experiments on Thai chickens demonstrated that with an increase in sperm motility, the activity of mitochondrial glutathione oxidase increases, and free radicals are neutralized (Toppo et al. 2009; Chauychu-Noo et al. 2021).

A decrease in selenium concentration during pregnancy reduces the activity of glutathione peroxidase and other antioxidant enzymes in blood plasma and erythrocytes. A significant decrease in glutathione peroxidase activity occurs during the first trimester and persists until the third with an additional slight fall during labor (Stoffaneiler and Morse 2015). Selenium deficiency in pregnant women may lead to the impaired development of the neural tube, and fetal growth restriction. Oxidative stress due to selenium deficiency may lead to miscarriages, premature labor, cholestasis, intrauterine growth retardation, preeclampsia, thyroid diseases, and diabetes mellitus.

Methods and methodology

Research methods used are the following: bibliosemantic, analytical, logical methods and generalizion method. The bibliographic database of life science and biomedical

information MEDLINE, EMBASE, Medline (PubMed), the Web of Science, and the Cochrane Central were searched for publications in English having the key words of this study. We used the following key words: [Selenium]; [antioxidants]; [neuroprotection], and [transcription factors]. All the authors independently selected articles, evaluated the quality of the data, presented and interpreted the data corresponding to the main idea of the study, and made up the final list of the references.

Conclusions

In recent years, the importance of selenium has been established for the prevention and management of viral infections. A relationship has been established between a decrease in selenoprotein levels and the incidence of coronavirus and HIV infection since the expression of pro-inflammatory interleukin-6 is increased in these diseases. Selenium is recommended for viral infections at a dose of 55 mcg per day. The non-pathogenic Coxsackie virus may turn into a pathogenic one when mice are kept on a low-selenium diet. Selenium deficiency can also significantly affect the survival of patients with HIV infection (Zhang and Liu 2020; Zhang et al. 2020).

A decrease in selenium levels in the body and the environment is known to increase mortality from AIDS and COVID-19 (Rayman 2012; Song et al. 2020; Zhang et al. 2020; Zhou et al. 2020), which is associated with the role of selenium as an antioxidant agent, as well as its action on gene activity in response to HIV or other viral infection.

Selenoproteins, first of all glutathione peroxidase, play an important role in the regulation of HIV manifestation. Proper selenium levels can delay the spread of the viral infections. A hypothetical HIV gene was cloned to prove the role of glutathione peroxidase in the prevention of viral infections, and that increased the synthesis of glutathione peroxidase. AIDS is often accompanied by lack of selenium, decreased numbers of T-helpers, or CD4 cells, and it is these lymphocytes that are the main target for HIV.

When searching for anticancer drugs, attention was drawn to organic and inorganic selenium compounds, which are liable to transformation. The mechanism of action of anticancer agents is mainly based on the induction of apoptosis in tissues and organs (Siegel et al. 2020). They can affect gene expression and various signaling pathways, DNA repair or damage (Tan et al. 2019), and the processes of angiogenesis and metastasis (Gandin et al. 2018). In this case, the metabolites of the compounds have high activity, which is associated with the formation of reactive oxygen species, which in turn lead to oxidative stress with the oxidation of the thiol groups of proteins in the cell (Harmanci et al 2017). Selenium and its compounds may have prooxidant and antioxidant properties. Besides apoptosis, selenium compounds may cause other types of cell death. The manifestation of oxidative stress is promoted by iron ions, which accumulate in the cell, undergo the Fenton reaction and contribute to the formation of free radicals. Iron also increases the activity of the enzyme lipoxygenase (Chen et al. 2020; Subburayan et al. 2020).

Selenium-dependent glutathione peroxidase is considered the main enzyme that prevents tumor development and is the main antitumor regulator. Ferroptosis can occur when the antioxidant defense of the cell is exceeded. Excessive production of free radicals damages DNA and activates the p53 protein. Cancer cell proliferation can be inhibited by suppressing NF-kB. Binding to DNA inhibits protein kinase P or histone deacetylase. Selenium can stop the cell cycle. There is evidence suggesting that selenite can induce necrosis in breast cancer cells (Chen et al. 2020; Zhang et al 2020). These data indicate that the trace element selenium is a significant factor for the health and normal metabolism of vital systems and organs. At the same time, abnormalities in its content in the body, pharmacokinetics and pharmacodynamics can contribute to the development of a wide range of diseases that requires adherence to certain doses when using selenium preparations.

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Conflict of interests

The authors declare no conflict of interests.

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