Selenium: From Health to the Biological Food Chain

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Selenium is an essential trace element which plays a role in the anti-oxidant activity in the cell. Selenium homeostasis needs to be strictly regulated as it can be harmful in excess or limiting amounts. Selenium has been studied extensively in its incorporation into seleneocysteine and subsequently seleneoproteins have been found in species ranging from algae to humans. Here within, a detailed review follows of selenium uptake within the human body and pathogenic implications. Also selenium toxicity will be examined in other organisms as well as its importance in biowebs and its role in the food chain. Lastly, the pathways of selenium in the cells will be discussed as well as future directions.

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Introduction

Selenium is a naturally occurring element that is crucial for the health and development of several organisms within the bioweb, from algae to humans [1-4]. Selenium can be found in nature in one of four oxidative states. The four inorganic states include elemental selenium (0), selenide (-2), selenite (+4), and selenate (+6) [5]; these inorganic forms of selenium are incorporated into various organisms and are frequently incorporated into proteins as the 21st naturally occurring amino acid known as selenocysteine, an analogue for cysteine. Interestingly, the codon that encodes for selenocysteine is UGA. This codon is commonly known as the "stop' codon [2]. However, under proper conditions, it is reinterpreted as the signal for selenocysteine. Proper factors required for this different interpretation of the signal include specific translations factor, a tRNA with a selenocysteine attached, and the biosynthetic equipment to synthesize the protein [3]. Because selenium has such profound effects within the finely balanced human system, it is of extreme importance that researchers have a more complete understanding of how this trace element is utilized, processed, the implications of deficiencies, as well as over exposure. Scientists are researching more basic organisms to understand how these systems incorporate selenium and how it affects them in order to gain insight into the applicability or benefit to humans as well as other organisms.

Toxicity of selenium

Selenium is a trace element required for several organisms, therefore there is a narrow range of exposure in which beneficial effects are exhibited [4, 6]. One of the main causes for the toxicity is propagation of selenium up the food chain due to the biotransformation from

inorganic to organic forms [4, 7, 8]. However, this transformation can be beneficial because of the crucial roles that selenium plays for various organisms.

Selenium toxicity is detrimental to the algae community due to the structures of the organisms that it affects. As stated, selenium poisoning induced both structural and functional damage [4, 9, 10]. These negative results were mostly seen as damage to chloroplasts. Within this study, the observed damages were the chloroplasts being granulous and exhibiting a less dense stroma than typically seen [4]. Furthermore, the thylakoid and pyrenoid were altered to the point of uselessness and a change in starch metabolism was observed as electron-dense deposits [10, 11]. Further induced damage included bleaching of the chloroplasts, an increase in the number of spines, and cell death [4, 6, 10, 12]. More specific verification of the damage to the chloroplasts was found using fluorescence. The chlorophyll fluorescence parameter F_v/F_m used indicated that the inorganic selenium damaged the structure of the PSII complex [4, 6]. The PSII complex is crucial in the production of ATP within plants, algae, and some bacteria [4, 13, 14, 15]. The formation of selnocysteine in the chloroplast was one of the proposed explanations for the damages observed at this site [11].

Other evidence of the negative effects of selenium was seen from the results of Geoffroy et al [4]. These results showed an inverse relationship between the population density of *C. reinhardtii* and ambient concentrations of selenate. Cellular diameter increases were also observed as a result of increasing amounts of selenate exposure. The cause for this increase was thought to be related to malfunction in the division process of the cells [4]. Overall, the study found that detrimental effects on the growth of the algae were observed starting at 2.4uM of selenate [4]. This value fell within the range of selenate measured for polluted sites [16, 17].

Selenium's activities in humans

Specifically for humans, it is required in trace amounts and exhibits protective effects such as defense against oxidative stress. Within humans selenium is mainly in the forms of selenoproteins that exhibit enzymatic redox activities [2, 3, 6]. The best understood redox activity of selenoproteins is the reduction of hydrogen peroxide and the detrimental lipid/phospholipid hydroperoxides into water and alcohols. The selenium-dependent glutathione peroxides (GPx) mediate this protective process and is one of several families of important selenoproteins within the body [18]. Furthermore, selenium aids in several critical metabolic pathways, antioxidant defense, and has roles within the immune system [3, 6, 18].

The way humans integrate selenium into their biological processes is via selenoproteins. Therefore, the focus of some research on humans has been on examining selenoproteins. It has been found that there are twenty-five genes within the human genome that have the ability to be translated into selenoproteins with discrete functions [2, 3, 19]. The roles of these various proteins within humans include protection from oxidative stress, a role in regulation of the immune system, disposal of damaging/signaling peroxides, regulation of redox signaling transport of selenium between the active sites of biosynthesis intracellular and intercellular, synthesis of selenocysteine, and

synthesis of structural proteins [3]. Relative to signaling within the cells, the primary activities of selenoproteins are carried out via thioredoxin reductases [3, 20]. Oxidative damage protection falls under the influences of several selenoproteins such as GPx, selenoproteins K, R, and W [3, 20].

Some examples of selenoproteins include three thyroid hormone de-iodinases and the three known thioredoxin reductases. The thyroid de-iodinases are accountable for activating the inactive form of thyroid hormone T4. The activation is achieved by the removal of iodine. The thioredoxin has involvement in both extracellular and intracellular regulation of the biosynthesis of deoxynucleotides and metabolism of the deoxynucleotides [3]. Glutathione peroxidases (GPx) are connected with catalyzing the reaction that reduces hydrogen peroxide and various organic hydroperoxides into water and the corresponding alcohols, which provides protection from oxidative damage. Selenoprotein K has antioxidant properties as well. This protein exhibits its function within the heart, skeletal muscles, pancreas, liver, and placenta. Selenoprotein R is a catalyst in the reduction of oxidized methionine, which is crucial for repairing oxidatively-damaged proteins [3, 21]. In the selenoprotein W, the function is not fully understood, however, high expression rates in proliferating myoblasts were observed [3]. Also in low concentrations the protein can be found in muscle tissue associated with white muscle disease in sheep and cattle [20].

Biowebs and exposure to selenium

This area is of interest because the base of our food chain can be greatly affected by selenium.

One of the global environmental issues at hand is selenium pollution [12]. In accordance with Geoffroy et al. [4], the devastating effects of selenium pollution was seen in levels beginning at 2.4 µM; this value is within the levels of selenate in known polluted areas [4]. Large-scale devastation to wildlife has occurred after a release of selenium into the environment including Belews Lake in North Carolina and Kesterson Reservoir and San Joaquin Valley, CA [11]. The consequences of the selenium poisoning were deformities and colossal reproductive failure, especially in the fish and bird communities [12, 22]. It did not require much additional selenium to be introduced into the ecosystem for these awful results to occur. For example, in the Kesterson Reservoir, the normal concentration of selenium was in the parts per billion; when there were devastating toxic issues, the levels had barely reached the micro molar levels [18]. This demonstrates the extreme sensitivity that creatures have regarding this vital element.

When primary producers were exposed to high amounts of selenium, the results observed were in structural and functional damage [4, 11]. It has been stated that one of the key points of grasping the effect on ecosystems, especially aquatic ecosystems, would be understanding how the organisms at the base of the food web, mainly micro algae, uptake selenium [11]. A direct correlation between the concentration of selenium in the water, as selenite, and the amounts of selenium within certain organisms has been shown [12, 9]. Selenite was of interest because this form is readily taken up from the water by algae and rapidly transformed into organo-selenium when compared to selenate [12]. Furthermore, since the algae are at the base of the food chain, there is the danger of poisoning of higher trophic levels due to

bioconcentration [4, 12]. These findings are supported by the research conducted by Morlon et al. [4] who concludes that the toxicity observed in higher trophic organisms within ecosystems that are contaminated with selenium is due to biomagnification. Furthermore, their research verified the roles of phytoplankton in the resulting bioaccumulation [4].

Uptake mechanisms

The two forms of selenium that are the most prevalent in ecosystems are selenate and selenite [4, 20]. Research has shown that there are varying toxicities associated with these different forms; for example, selenite is more toxic to organisms than selenate [6]. This difference stems from the ability of the algae to uptake the selenium [4]. According to the findings of Morlon et al. [12] it is thought that algae has two mechanisms of transport for selenite, the one used depends upon the concentration of selenite in its environment. At low concentrations, the mechanism of transport is specific and involves a high- affinity for the micronutrient. At high concentrations, the transport system is suggested to be less specific and is further altered with the addition of sulfate and nitrate ions [12]. Furthermore, the method of transport follows Michaelis-Menten kinetics, one pathway with low concentrations and one pathway with high concentrations [12]. Specifically, research conducted by Umysoca et al. [6] has shown that in *Chlaymdomonas reinhardtii,* selenite had a specific mode of transport in low concentrations, yet at high ambient concentrations of selenite it was incorporated into the cell non-specifically. Mechanisms of uptake, specific or non-specific, for selenium are existent because the simple diffusion of a selenium ion into the cell is highly

unlikely [12]. Therefore, it has been thought that either anion/proton symport or anion/ anion antiport mechanisms are probable [12].

Further evidence for non-specific transport were studies that showed that certain oxyanions had an antagonistic effect, this means there was competition for the same pathways of uptake between selenite and these oxyanions such as sulfate, phosphate, nitrate, and bicarbonate salts. This inhibition was due to the chemical similarities, especially between selenite and sulphur Morlon, et al. have shown that by increasing the concentrations of sulphate, the uptake of selenite would be inhibited in *C. reinhardtii*; these findings were indicative of a common, non-specific pathway of uptake in which sulphur would be favorably incorporated over selenium [12].

Selenium deficiency: diseases and disorders

There are several areas of the world that are selenium deficient including UK, New Zealand and North-East China [3]. The current daily recommendations for the levels of selenium are based on the amount required for maximal GPx activity [3]. Everyday foods that are found in the United States contain levels of selenium that would allow for adequate consumption to meet the recommended daily amount. Some common foods that contain higher amounts of selenium include Brazil nuts, tuna fish, beef, and spaghetti [24]. However, when the food that a country's population is consuming is inadequate in providing the proper levels of selenium, selenium deficiency results.

For example, there is a region in China where the soil is selenium deficient [18]. Because the soil is lacking the adequate amounts of selenium, the food grown is lacking, and the

animals that eat the food lack the normal amounts of selenium. Therefore, there is widespread occurrence of diseases and other health issues related to selenium deficiency. In 2008, it was estimated that there were about 0.5 to 1.0 billion people worldwide that had an inadequate intake of selenium in their diets [3]. Some of the diseases observed related to selenium deficiency were Keshan disease, Kashin-Beck disease, Myxedematous Endemic Cretinism, as well as male infertility [3]. Keshan disease is a congestive cardiomyopathy disease, Kashin-Beck disease results in deforming arthritis, and Myxedematous Endemic Cretinism leads to mental retardation [18]. Lack of selenium results in male infertility because selenium is required for the normal development and formation of the spermatozoa [18, 25]. Some studies have been conducted to understand the role that selenium has within the male fertilization process. One such study fed a group of male horses a diet that was deficient in selenium. The sperm were examined and were found to have structural abnormalities. These irregularities were seen in the midpiece of the sperm, which resulted in poor motility as well as a tendency for the tail to become detached. These deviant structures resulted in a decrease in the probability of fertilization [18]. The cause for the malformation at the midpiece region was due to the lack of protection from oxidative damage by a form of GPx (GPx4). This protein normally develops into a structural protein in mature spermatozoa in the mitochondria capsule [18]. Therefore, it was clear why the motility would decrease. If the mitochondria center of the sperm was compromised, it would be unable to produce the energy required for propelling itself. The work and interpretation done by Usini and colleagues was supported by the work and conclusions of the Glasgow Royal Infirmary

[18, 26].

Selenium and the immune system

There has been a strong focus of research on how selenium interacts with the human immune system, especially since the discovery of considerable amounts of selenium in important tissues associated with the immune system [3, 18, 20]. These tissues include the liver, spleen, and various lymph nodes. The immune system is a very complex and elegant system that involves many levels of activation and stimulations for the end result to occur. Selenium has a vital role within this complex orchestration of effectors and receptors because studies have shown it to have an influence in all parts. In addition, it is known that selenium has the ability to aid in the response to infections and to cancer by up-regulating the immune system [3].

Specifically, Kiremidjian-Schumacher et al. has reported that 200 mg/day of selenium can result in considerable immunoenhancing benefits. However, this must be done with caution because selenium is highly toxic and has a narrow range of beneficial results [18, 27]. Nevertheless, the benefits shown through research were astounding. One study, using selenium supplementation with animal models, found that there was an increase in T-cell proliferation responses, lymphokine-activated killer cell activity (a white blood cell that has been activated to kill cancer cells), natural killer cell activity, and the responsiveness to vaccines [3, 28]. One study with human patients saw an increase in GPx activities and an increase in the number of total T-cells with a supplement of 100mg/day of selenium [3]. An example of the increase in vaccine responsiveness: subjects who were supplemented with selenium were

immunized with a live attenuated polio vaccine and were shown to have a rapid clearance of the poliovirus [3]. Dietary supplementation has also indicated an increase in natural killer cell function in the elderly [3]. Kiremidjian-Schumacher's work has also shown that there was an 82% increase in natural killer-cell activity with supplementation of selenium, as compared with a base-line control group. The immune boost exhibited by selenium is thought to be due to the apparent control selenium has on the mechanism of up regulation for the expression of growth-regulatory cytokine interleukin-2. This complex appears on the surface of activated lymphocytes and natural killer cells. That is important because it facilitates the interaction with IL-2, which is required for the differentiation into cytotoxic T-cells to occur [18, 27].

Just as supplementation can result enhance immune system response; selenium deficiencies can hinder the immune system. For example, with an inadequate intake of selenium there can be a reduction in the effectiveness of neutrophils, T-cell counts, differentiation of T-cells, IL-2 affinity, natural killer cell activity, and antibody response [3, 27]. This was why there have been several outbreaks of severe diseases and other medical issues within areas of the countries with selenium deficiencies, as previously noted. Beck and colleagues have documented the detrimental effects of selenium deficiency via experiments with mice [26, 30]. This experiment was of particular interest because the situation created and observed was thought to be linked to the development of Keshan disease [27, 31]. They showed that within a selenium-deficient host, a harmless virus could become virulent. Within the selenium deficient mouse, the benign Coxsackie's virus mutated at six separate points,

resulting in a cardio virulent form; these mutations yielded myocarditis with similarities seen in humans. When a mouse with adequate amounts of selenium was inoculated with the mutated virus, heart damage still resulted. This showed that the mutations that occurred to the virus within the deficient mouse were irreversible [29]. Because damages done to viruses were irreversible, it proved the extent in which selenium provides protection [29-31].

In addition to the evidence shown about the Coxsackie's virus, selenium has been shown to be a crucial nutrient for Human Immuno-deficiency Virus (HIV) [18, 29, 30]. However, the relationships between virus and selenium levels were different. In the case of the Coxsackie's virus, the propagation and severity of the mutations to the virus were due to the host being deficient in selenium prior to exposure to the virus. Yet with HIV, the depressed levels of selenium might not be a contributing factor to the progression of the disease, but a result of the disease [18, 29]. Nevertheless, this creates a downward spiral in that the disease first creates the selenium deficiency which in turn results in a weakened immune system that the virus is able to take advantage of, thus exacerbating the progression of the disease. There have been more than twenty papers published reporting the parallel between the decline in plasma selenium and the loss of CD-4 T-cells within individuals infected with HIV; therefore, it was commonplace to think of the loss of CD-4 T-cells as the progression of HIV [18, 32]. This decline was even apparent in the early stages of the virus, before malnutrition as a result of malabsorption was a factor [18].

Selenium and cancer

One of the most active areas of current

investigations with selenium supplementation is in the protective actions of selenium against cancer. Since the 1970's, epidemiological studies have shown that there was an inverse relationship between cancer mortality and levels of selenium ingested [18, 33]. Some speculations as to the protective actions are that selenium has an ability to up-regulate immune response. Another theory is that selenium possesses the ability to construct anit-tumoregenic metabolites, for example methyl selenol or its precursors. These metabolites are able to alter the metabolism of the tumor cell, inhibit angiogenesis, and ultimately induce apoptosis of the cancer cells. Inhibition of angiogenesis is a vital ability in the protection against growth of a tumor cell because angiogenesis is the creation of new blood vessels into the cancerous mass [34]. By having the ability to prevent the creation of this new network of blood vessels, the body has the power to cut off both the supply of nutrients and the ability to remove wastes from the tumor. Effectively, it is like an army laying siege to a city: without a supply of nutrients and a way to remove the waste, the inhabitants starve and decay in their own toxins.

The first double-blind, placebo-controlled intervention trial that was conducted on a western population was carried out by Clark and co-workers in the United States, and it was known as the Nutritional Prevention of Cancer (NPC) Trial [35]. The researchers were testing the hypothesis that the incidence of cancer could be reduced with supplementation of selenium. The trial included 1,312 individuals who were without a history of the skin cancer melanoma. These people were randomized into either a placebo group or a group that received 200mg of selenium yeast (recall that this was also the amount deemed to result in a noticeable boost in immune function). While there was not an effect on the development of melanoma, there were several noteworthy observations. For example, Clark noted that the cancer mortality rate decreased by 50% and the total cancer incidence diminished by 37%. Furthermore, there were 63% less cases of prostate cancer, cancers of the colon were 58% fewer, and cancers of the lung were reduced by 46% [18, 35]. These findings are astounding; with promising results such as these, it is understandable that there would be such great interest in trying to further understand the role that selenium has within the human immune system as well as within other organisms.

Conclusions

Researchers know that selenium is a vital component to health, and that deficient amounts and over-exposure are both detrimental to the well-being of organisms. Therefore, to gain a better understanding of how these processes work, it is best to start at the base of the food chain and with less complex organisms. Researchers have discovered selenium containing proteins in humans; rodents, green algae, fish, amoebae, nematodes, parasites, insects and other crustations [2]. However, understanding how selenium is regulated within these organisms is still not clear. In the future, more detailed selenium homeostasis studies seem critical in order to address how cells handle their levels of selenium.

Acknowledgements

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