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Introduction: the selenium conundrum

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Abstract. Selenium was first suspected of being an essential dietary trace element in the 1950s. We now know that indeed it is an essential biological element that serves as an integral component of several enzymes, including those in the families of deiodinases and glutathione peroxidases as well as selenoproteins P and W. The multi-author review that follows this introduction concentrates on the important biological role of selenium in enzymes as well as some of the physiological aspects of selenium as either a potential anticarcinogenic agent or insulin mimetic. What should become clear from these contributed articles is the complex and dynamic role that selenium plays in many biological processes and that the investigations in these areas are at the edge of exciting new frontiers.

Key words. Selenium; deiodinases; glutathione peroxidases; selenoprotein P; selenoprotein W; anticarcinogenic agent; insulin mimetic.

Chemically, selenium, a group VIA member, is typically defined as nonmetallic, although one of its allotropes has a metallic appearance and is a semiconductor. Selenium is quite rare and occurs mainly as an impurity in sulfur, sulfide and sulfate deposits. It is obtained from flue dusts that result from roasting sulfide ores and from the anode mud formed in the electrolytic refining of copper. Selenium has long been used in glass making. Particles of colloidally dispersed selenium give a ruby-red coloring in glass. Selenium is also considered an important element in modern technology because of its semiconductor properties. The gray crystalline allotropic form of selenium that has the electrical conductivity property is very light sensitive and thus is used successfully commercially in such things as photocopy machines and solar cells.

Biologically, selenium was first suspected of being an essential dietary element in the 1950s. We now know that indeed it is an essential biological trace element that serves as an integral component of several enzymes, including those in the families of deiodinases and glutathione peroxidases as well as selenoprotein P and W (see articles in this multi-author review). In recent years, selenium has also been touted to be important as an antioxidant, anticarcinogenic agent and insulin mimetic (see articles in this review). Dietary selenium, which comes mainly from the foods that we eat, is highly variable and dependent on the selenium content of the soil. In areas of the world where selenium content of the soil is low, selenium deficiency can arise in the population. For example, selenium deficiency is a major public health problem in certain parts of China, where it increases the risk of heart disease, bone and joint disorders and liver cancer.

Despite the essentiality of this nutrient, selenium can produce a host of toxic events in a wide variety of cell types, including hepatocytes, erythrocytes and lymphocytes. In animals, Se toxicity produces conditions known as 'blind staggers' and 'alkali disease' due to cattle grazing on grass growing in soil with a high selenium content. Selenium can also profoundly affect the overall tyrosyl phosphorylation state of the cell, suggesting that signaling cascade control of physiological processes may be hindered in the presence of high levels of selenium. These toxic effects of selenium are thought to be mediated through the generation of reactive oxygen species by depleting glutathione and protein-bound sulfydryl groups, although other mechanisms may be possible.

Thus, from above, it is clear that the role of selenium is indeed a conundrum and to adequately cover all its potential roles would be difficult to do in this or any

other multi-author review. Therefore, we have attempted to focus on some of the recent exciting discoveries in regard to the more common positive physiological aspects of selenium as either a potential anticarcinogenic agent, insulin mimetic or essential component of some enzymes. As indicated in the contribution by J. R. Arthur, it was shown in the early 1970s, that selenium is a critical component of glutathione peroxidase (GPX-1). This enzyme is involved in the removal of peroxides and serves as part of an organism's antioxidant defense system. Since the initial discovery, three other glutathione peroxidases (GPX 2–4) have been identified and characterized, all of which contain selenocysteine at the active site. Whereas numerous studies throughout the years have concentrated on the role of glutathione peroxidase in various disease states and on its regulation by selenium concentration, Arthur's review focuses on those studies that have utilized such molecular techniques as overexpression studies or knockout methods to define the function of glutathione peroxidases.

Another selenium-containing protein that maybe involved in oxidant defense is selenoprotein P. Selenoprotein P, as described in the review by Moschos and Akesson, is a ubiquitously expressed, extracellular glycoprotein that may contain up to 10 selenocysteine residues. Selenoprotein P binds to heparin and cell membranes, and in human plasma protects against the peroxynitrite-mediated oxidation. The characterization of white muscle disease led to the discovery of yet another selenium-containing protein that may be involved in the antioxidant function of a cell. Selenoprotein W, as reviewed by P. D. Whanger, is found in highest concentration in the muscle, heart and brain of sheep and primates, and its level in these tissues is influenced by selenium concentration. Whereas the exact metabolic function of selenoprotein W is still not clear, it is interesting to note that this protein can bind glutathione, an important peptide in the natural defense mechanism of a cell. Additionally, selenoprotein W binds an unknown 41-kDa moiety. This unknown moiety has a sequence that resembles a calcium binding domain, however, more extensive studies are needed to completely define its role.

Another interesting set of selenium-dependent proteins are the deiodinases, a family of enzymes that exert tight control on local and systemic availability of active thyroid hormone (T3). Currently, as described in the review by J. Kohrle, there are at least three deiodinase enzymes (type I, II and III) which show different biochemical and regulatory characteristics as well as different tissue distribution and developmental patterns of expression. In his review, Kohrle details the structure, function and molecular characteristics of these enzymes. Interestingly, only type I 5′ deiodinases have clearly been shown to have selenium-dependent expression. Type II and III 5′ deiodinase show limited response to variations in selenium concentration, and thus the role of selenium still needs to be attained.

Use of selenium as a nutritional supplement has been popularized recently due to its potential role in low concentrations as an antioxidant and in higher concentrations as an anticarcinogenic agent. The anticarcinogenic properties of selenium, as described in the review by G. N. Schrauzer, are well supported by a variety of data obtained from not only animal studies but also ecological and epidemiological ones. The anticarcinogenic actions of selenium occur at the systemic, cellular and nuclear level. They may also involve the immune system. Many of the protective effects appear to be associated with glutathione peroxidase, a critical enzyme in the natural defense mechanism of a cell; however, multiple mechanisms most likely are involved.

Selenium, as indicated in the review that I have contributed, has also been reported to act as an insulin-mimetic agent with regard to normalization of blood glucose levels and regulation of some insulin-mediated metabolic processes. As in the case of selenium as an anticarcinogenic agent, the mechanism by which selenium is capable of mimicking insulin is not clear. Several studies, however, note that selenium does activate key proteins involved in the insulin-signal cascade. While various proteins in the insulin-signal cascade have been shown to be necessary for different insulin-regulated events, these data are not yet quite clear in regard to selenium.

It should be clear from the topics and scope of this multi-author review that the biological role of selenium is complex, diverse and intriguing. As investigators in this field, we hope you find this review of value and significance. We look forward to the many challenges that this field offers and to the new and exciting discoveries of our colleagues, in particular to the mechanistic role that selenium takes on as an integral component of some enzymes, and in its physiological role as an anticarcinogenic agent and insulin mimetic.

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