Selenium in the Immune System[1,2]

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ABSTRACT Selenium as an essential component of selenocysteine-containing protein is involved in most aspects of cell biochemistry and function. As such, there is much potential for selenium to influence the immune system. For example, the antioxidant glutathione peroxidases are likely to protect neutrophils from oxygen-derived radicals that are produced to kill ingested foreign organisms. When the functions of all selenoproteins are described, only then will it be possible to fully understand their role in maintaining optimal immune function. J. Nutr. 133: 1457S–1459S, 2003.

KEY WORDS: • *selenium* • *immunity* • *neutrophils*

Selenium is essential for the efficient and effective operation of many aspects of the immune system in both animals and humans. Immunity and the immune system are a very complex collection of processes that act together to protect organisms against attacks by pathogens and malignancy. Many immune functions involve inflammatory mechanisms that when uncontrolled may be implicated in the pathogenesis of conditions such as coronary heart disease, cancer, immunity and rheumatoid arthritis. The cellular biochemistry of selenium is also a complex system that involves the expression of a wide range of selenium-containing proteins many of which remain to be characterized (1,2). Selenium is found in varying quantities in the rocks and soils of different regions of the world. In these areas, this is reflected in the differing amounts of selenium in forage crops and diets and in the animals and humans that consume locally produced foods. There is much debate as to whether the modification of selenium status of humans can be associated with an altered incidence and/or increased susceptibility to many diseases. There is no doubt, however, that low dietary intakes of selenium and consequent deficiencies in farm animals can result in a wide range of diseases that are often associated with a concurrent vitamin E deficiency (3,4). Many of these conditions have been reproduced experimentally in farm animals and rodent models. Such experiments were often carried out to try and understand the mechanism whereby lack of selenium was involved in the pathogenesis of diseases. Thus, the association of selenium deficiency with vitamin E deficiency led to hypotheses that relied on oxidant/antioxidant processes (5). The antioxidant effects of selenium were suggested to be mediated through the glutathione peroxidases (GPx)[4] that removed potentially damaging lipid hydroperoxides and hydrogen peroxide. At least five of these peroxidases have now been identified as operating in different cell and tissue compartments (6,7). Thus, selenium can act as an antioxidant in the extracellular space, the cell cytosol, in association with cell membranes and specifically in the gastrointestinal tract, all with potential to influence immune processes. Additionally, thioredoxin reductases that contain selenium may also act as antioxidants (8).

Other selenoproteins are involved in many other aspects of cell metabolism, which increases the potential for recognition of adverse effects of selenium over and above those caused by antioxidant systems. More than 20 selenoproteins have been characterized by purification, cloning, recombinant expression and prediction of function using bioinformatic techniques. In total, 25 genes that code for selenoproteins have been detected in the human genome. Thus, several of the > 30 proteins that are labeled by ^{75}Se in animals and cells must be due to alternative splicing (1,2,9). As well as GPx, selenoenzymes form families of three thioredoxin reductases and three iodothyronine deiodinases. These give selenium essential functions in redox control of many metabolic functions in cells (in particular transcription factors) as well as in thyroid hormone metabolism. Other selenoproteins that may have antioxidant functions are selenoproteins P and W. With re-

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[4] Abbreviation used: GPx1, cytosolic glutathione peroxidase.

spect to immune function, there is also a specific 15-kDa selenoprotein that has been identified in T cells, although its exact function is unknown. Another selenium-containing protein is selenophosphate synthetase, which catalyzes the production of selenophosphate. This selenophosphate is an essential inorganic precursor for the synthesis of selenocysteine from serine during selenoprotein synthesis. The families of selenoproteins that are discussed above are candidates for the involvement of selenium in the immune system. Details of these and other selenoproteins are discussed in several reviews (1,2,6,9,10).

Thus, via the selenoproteins, selenium can influence three broad areas of cell function through antioxidant activities, thyroid hormone metabolism and regulation of the activity of redox-active proteins (10). All of these general effects on metabolism can be associated with more specific processes that will affect the immune system. Clearly, therefore, the influence of selenium on the immune system is multifactorial, and particular circumstances determine which systems are affected.

Selenium and the immune system

Dietary selenium is essential for an optimum immune response, although the mechanisms of this requirement are not always fully understood. Selenium influences both the innate, "nonadaptive" and the acquired, "adaptive" immune systems (3,11,12–17). The innate immune system includes barriers to infection and nonspecific effector cells such as macrophages. Both the T and B lymphocytes form the major effector cells of the acquired system that mature with exposure to immune challenges. Selenium-deficient lymphocytes are less able to proliferate in response to mitogen, and in macrophages, leukotriene B4 synthesis, which is essential for neutrophil chemotaxis, is impaired by this deficiency. These processes can be improved by selenium supplementation. The humoral system is also affected by selenium deficiency; for example, IgM, IgG and IgA titers are decreased in rats, and IgG and IgM titers are decreased in humans. In endothelial cells from asthmatics, there is a marked selenium deficiency that results in an increase in expression of adhesion molecules, which causes greater adhesion of neutrophils. These and many other effects of selenium on the immune system have been reviewed in recent publications (3,11,12–17), and here we consider only some effects on neutrophil function in more detail.

Selenium and neutrophil function

One of the most widely investigated associations between selenium and the immune system is the effect of the micronutrient on neutrophil function. Neutrophils produce superoxide-derived radicals to take part in killing of microbes. This type of process is a balance between the production of sufficient radicals to kill invading organisms and the systems that protect the neutrophils themselves from the radicals. Thus, although selenium deficiency does not affect neutrophil numbers in a range of species, certain aspects of their function are defective (3). Neutrophils from selenium-deficient mice, rats and cattle are able to ingest pathogens in vitro but are less able to kill them than are neutrophils from selenium-sufficient animals (18). This defective function has been associated with decreased cytosolic GPx (GPx1) activity in the neutrophils, which allows the free radicals that are produced in the respiratory burst to kill the neutrophils themselves. Examination of the rate of radical production in stimulated neutrophils from mice supports this hypothesis (**Table 1**). The initial rate of reduction of cytochrome c by neutrophils stimulated with phorbol myristate acetate was the same in selenium-deficient mice or mice repleted by IP injection with between 2.5 and 1,000 μg of selenium/kg bodyweight. However, only the neutrophils from the selenium-repleted animals were able to continue producing the radicals for $>$ 10 and $\leq$ 45 min. The ability to continue to produce radicals depends on increased selenium status and GPx activity in the neutrophils (**Fig. 1**). Neutrophil candidacidal activity had a biphasic pattern. At very low doses of selenium given to deficient mice, candidacidal activity increased from ~9 to 14%. Additional selenium supplementation did not increase this activity until much higher doses were given, which also correlated with changes in the GPx activity (Fig. 1). The conclusions from these studies are that there is more than one selenium-dependent function or intracellular compartment that regulates the ability of immune cells to kill ingested organisms. Part of this is due to GPx1 activity. Additional work is required to determine whether the initial changes in candidacidal activity are dependent on phospholipid hydroperoxide GPx activity and a specific pool of GPx1 or cytosolic or mitochondrial thioredoxin reductase.

Selenium, neutrophil function and cell metabolism?

It must be emphasized that the data shown in Table 1 and Figure 1 were obtained using in vitro cultures of neutrophils. Their function in vivo might also be modulated by other factors including thyroid hormone metabolism, which is impaired in selenium deficiency. Hypothyroidism has adverse effects on immune function; it generally impairs the ability of neutrophils to respond to a challenge or to foreign organisms. Stress may influence thyroid function through suppression of thyroid hormone metabolism. Thymus contains type 2 iodothyronine deiodinase activity, which is generally confined to tissues that require local production of triiodothyronine from thyroxine for optimal activity (19). Any impairment of type 2 deiodinase activity in selenium deficiency could have effects on the immune system through suboptimal development and function of thymic cells. As well as killing invading pathogenic bacteria

TABLE 1

Superoxide production by mouse neutrophils[1]

Selenium, μg of selenium/kg body wt	ΔOptical density · min^{-1} · 10^{-6} cells		Duration of cytochrome c reduction, min
	10–30 min	≤10 min	
0	0.081 ± 0.010	0	< 10
2.5	0.069 ± 0.013	0	< 10
6	0.076 ± 0.008	0	< 10
8	0.084 ± 0.012	0.005 ± 0.003	< 10
10	0.080 ± 0.016	0.007 ± 0.003	< 12
20	0.072 ± 0.009	0.007 ± 0.001	< 15
50	0.074 ± 0.014	0.012 ± 0.001	< 30
100	0.071 ± 0.008	0.024 ± 0.001	> 45
200	0.091 ± 0.010	0.028 ± 0.006	> 45
500	0.081 ± 0.013	0.024 ± 0.005	> 45
750	0.073 ± 0.011	0.028 ± 0.003	> 45
1,000	0.080 ± 0.013	0.032 ± 0.003	> 45
Se-supplemented control	0.083 ± 0.010	0.045 ± 0.002	> 45

[1] Mice were made selenium deficient and then repleted with selenium as described in Figure 1. Five days after treatment, neutrophils were obtained from the peritoneal cavity of the animals and incubated in a balanced salt solution and their superoxide dismutase-sensitive ability to reduce cytochrome c ΔOD 550 nm in response to stimulation with phorbol myristate acetate (1 mg of phorbol myristate acetate/mL in 10 μL of DMSO per 3-mL incubation) was determined (18). Results are means ± SEM; 5–7 animals per group.

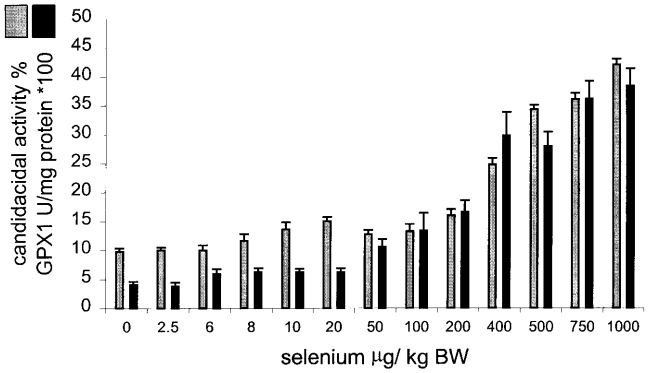

FIGURE 1 Cytosolic glutatione peroxidase (GPx1) activity and candidacidal activity in neutrophils from selenium-deficient mice treated for 5 d with different doses of selenium. Mice were made selenium deficient using the protocols and diet described previously (18) and where indicated were treated with selenium as sodium selenite in 0.9% NaCl by intraperitoneal injection. Five days after treatment, neutrophils were obtained from the peritoneal cavity of the animals and incubated in a balanced salt solution and their candidacidal activity was determined (18). Increases in activities in groups treated with > 10 μg of selenium/kg body wt were statistically significant with $P < 0.05$ or better (ANOVA and test of least-significant difference). Results are means $\pm$ SEM for 5–7 animals group.

and fungi, selenium is also essential for other aspects of cell-mediated immunity. This includes removal of viruses and destruction of neoplastic cells. Possible mediators of these selenium functions are the GPx, although this cannot all be directly related to protection against peroxides (13,14). Equally, however, the GPx and perhaps the thioredoxin reductases may influence eicosanoid metabolism to modulate inflammation and chemotactically active compounds. Fatty acids of the (n-3) and (n-6) series act as substrates for the lipoxygenase and cyclooxygenase pathways; the former give rise to the leukotrienes, which are proinflammatory and the latter the prostaglandins and thromboxanes (13,20). Selenium deficiency can favor the formation of proinflammatory compounds that would predispose toward diseases such as heart disease and cancer.

Adequate dietary selenium is essential for the activity of virtually all arms of the immune system. It is particularly significant that supplemental selenium can improve immune function in British individuals who consume diets that are considered adequate by World Health Organization (WHO) criteria but do not meet the British Recommended Daily Intake (21).

LITERATURE CITED

1. Kryukov, G. V. & Gladyshev, V. N. (2002) Mammalian selenoprotein gene signature: identification and functional analysis of selenoprotein genes using bioinformatic methods. In: Methods in Enzymology 347 (Sies, H. & Packer, L., eds.), pp. 84–100. Academic Press, San Diego, CA.

2. Lescure, A., Gautheret, D. & Krol, A. (2002) Novel selenoproteins identified from genomic sequence data. In: Methods in Enzymology 347 (Sies, H. & Packer, L., eds.), pp. 57–70. Academic Press, San Diego, CA.

3. Turner, R. J. & Finch, J. M. (1991) Selenium and the immune response. Proc. Nutr. Soc. 50: 275–285.

4. Wichtel, J. J. (1998) A review of selenium deficiency in grazing ruminants part 1: new roles for selenium in ruminant metabolism. N. Z. Vet. J. 46: 47–52.

5. Walsh, D. M., Kennedy, D. G., Goodall, E. A. & Kennedy, S. (1993) Antioxidant enzyme activity in the muscles of calves depleted of vitamin E or selenium or both. Br. J. Nutr. 70: 621–630.

6. Arthur, J. R. (2000) The glutathione peroxidases. Cell. Mol. Life Sci. 57: 1825–1835.

7. Pfeifer, H., Conrad, M., Roethlein, D., Kyriakopoulos, A., Brielmeier, M., Bornkamm, G. W. & Behne, D. (2001) Identification of a specific sperm nuclei selenoenzyme necessary for protamine thiol cross-linking during sperm maturation. FASEB J. 15: 1236–1238.

8. Miller, S., Walker, S. W., Arthur, J. R., Nicol, F., Pickard, K., Lewin, M. H., Howie, A. F. & Beckett, G. J. (2001) Selenite protects human endothelial cells from oxidative damage and induces thioredoxin reductase. Clin. Sci. (Lond.) 100: 543–550.

9. Hatfield, D. L. & Gladyshev, V. N. (2002) How selenium has altered our understanding of the genetic code. Mol. Cell. Biol. 22: 3565–3576.

10. McKenzie, R. C., Arthur, J. R. & Beckett, G. J. (2002) Selenium and the regulation of cell signaling, growth, and survival: molecular and mechanistic aspects. Antioxid. Redox Signal. 4: 339–351.

11. Kiremidjian-Schumacher, L. & Roy, M. (1998) Selenium and immune function. Z. Ernahrungswiss. 37: 50–56.

12. McKenzie, R. C., Rafferty, T. S., Arthur, J. R. & Beckett, G. J. (2001)Effects of selenium on immunity and ageing. In: Selenium: Its Molecular Biology and Role in Human Health (Hatfield, D. L., ed.), pp. 258–272. Kluwer Academic Publishers, Boston, MA.

13. McKenzie, R. C., Arthur, J. R., Miller, S. M., Rafferty, T. S. & Beckett, G. J. (2002)Selenium and the immune system. In: Nutrition and Immune Function (Calder, P. C., Field, C. J. & Gill, N. S., eds.), pp. 229–250. CAB International, Oxford, U.K.

14. Beckett, G. J., Arthur, J. R., Miller, S. M. & McKenzie, R. C. (2003) Selenium, immunity and disease. In: Dietary Enhancement of Human Immune Function (Hughes D. A., Bendich, A. & Darlington, G., eds.). Humana Press, Totowa, NJ (in press).

15. Brown, K. M. & Arthur, J. R. (2001) Selenium, selenoproteins and human health: a review. Public Health Nutr. 4: 593–599.

16. Bhaskaram, P. (2002) Micronutrient malnutrition, infection, and immunity: an overview. Nutr. Rev. 60: S40–S45.

17. Spallholz, J. E. (1990) Selenium and glutathione peroxidase: essential nutrient and antioxidant component of the immune system. Adv. Exp. Med. Biol. 262: 145–158.

18. Boyne, R. & Arthur, J. R. (1986) The response of selenium deficient mice to *Candida albicans* infection. J. Nutr. 116: 816–822.

19. Molinero, P., Osuna, C. & Guerrero, J. M. (1995) Type II thyroxine 5′-deiodinase in the rat thymus. J. Endocrinol. 146: 105–111.

20. Werz, O., Szellas, D. & Steinhilber, D. (2000) Reactive oxygen species released from granulocytes stimulate 5-lipoxygenase activity in a B-lymphocytic cell line. Eur. J. Biochem. 267: 1263–1269.

21. Jackson M. J., Broome, C. S. & McArdle, F (2003) Marginal Dietary Selenium Intakes in the UK: Are There Functional Consequences? J. Nutr. 133: 1557–1559.