Selenium and Inflammation: Underlying Anti-inflammatory Mechanisms

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Abstract

The essential trace element selenium (Se), in the form of selenoproteins, plays a pivotal role in the antioxidant defense system of the cell. There is evidence that Se may confer benefits in patients with inflammatory disease and even infectious diseases like HIV. Furthermore, in patients with severe sepsis, characterized by an increase in reactive oxygen species and low endogenous anti-oxidative capacity, as well as in patients with systemic inflammatory response syndrome, Se supplementation may reduce mortality and improve the clinical outcome, respectively. The nuclear factor kappa-B (NF-κB) signaling pathway has been associated with enhanced inflammatory response and its activation has been significantly correlated with interleukin-6 and TNF-α production. Selenium may inhibit the activation of NF-κB by modulating selenoprotein genes expression. Moreover, Se supplementation in chronic inflammation restores the depleted hepatic and serum Se levels by increasing selenoprotein biosynthesis leading to suppressed CRP production thereby attenuating the inflammatory process. Se increases shedding of L-selectin from monocytes while decreasing soluble L-selectin, which has been reported to be associated with high mortality in patients with sepsis. These mechanisms are likely to contribute to the modulatory effects of an increased Se status on the inflammatory response. This review evaluates some apparently key mechanisms of the anti-inflammatory action of selenium and advocates Se supplementation as a modulator of inflammatory response in infectious and autoimmune disease. Prospective, randomized, controlled studies must be performed to provide a greater degree of certainty.

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Introduction

Selenium (Se) is a unique trace element present in selenoproteins (SePs) in the form of selenocysteine (Secys). The 21st amino acid Secys is co-translationally incorporated within UGA codons in combination with 3-utr Secys-insertion sequence (SECIS). SeP biosynthesis and function are essential for maintaining human and animal life [1]. Cellular glutathione peroxidase (GPX) was the first enzyme to be characterized as SeP, thereby enabling further research, which identified Se as a major antioxidant element acting via enzymes that catalyze redox reactions [2]. Moreover, the identification of type I iodothyronine deiodinase as SeP was the breakthrough for establishment of the link between Se and thyroid hormones [3].

Se has been revealed as a regulator of thyroid hormone metabolism [4], while several interventional studies over the last few years have documented a variable decrease of anti-TPO levels in patients with autoimmune thyroiditis (AIT) treated with Se supplementation [5–8]. Furthermore, Se administration in pregnant women with AIT may prevent hypothyroidism and impede the manifestation of postpartum thyroiditis by suppressing the anti-TPO levels [9]. It has therefore been theorized that Se, as an essential component of the antioxidant enzyme system, may have an important role in AIT by modulating the immunological parameters [10]. The effects of Se supplementation are probably dependent on its serum basal levels. The lower the levels the better is the therapeutic response, as has been shown in a recent study from Austria conducted in a small number of young patients with AIT and very low basal Se levels [11]. Although the normal levels are wide, usually ranging from 40–140 mg/l, a Se concentration of about 80–90 µg/l

is considered adequate for SeP synthesis and activation, while levels of about 100–114 mg/l have been evaluated as being effective for maximal GPx activities [12]. In contrast, levels considerably above 200 µg/l may induce several adverse effects, including a pro-oxidant impact.

Beyond its immune regulating properties, Se may counteract oxidative stress induced by inflammatory or viral infectious diseases [13]. The aim of this review is to emphasize the anti-inflammatory effects of Se and to offer a comprehensive overview of the mechanisms of these anti-inflammatory actions.

Proinflammation

Proinflammation is a common biological phenomenon providing first-line defense against infection or invasion of pathogenic biological agents such as viruses, bacteria, and parasites [14]. By combating the intrusion of invaders, proinflammation narrows down the 'battlefields' in an attempt to contain any disease-related detrimental impact. However, should the balance between pro- and anti-inflammatory mechanisms be disrupted, proinflammation may lead to wide-ranging detrimental effects. Although it is not as yet determined if proinflammation constitutes a general pathophysiological background of disease, it has been accepted as a common denominator of an array of chronic immunological diseases [15].

Nuclear Factor-κB Cascade

Activators of the proinflammatory process, including stress response, free radicals, oxidative stress, bacterial, and virus infections, facilitate disease manifestation via activation of the nuclear factor-kappaB (NF-κB) pathway [16]. NF-κB is a transcriptional factor of pivotal importance in immune and proinflammatory response, having been associated with enhanced inflammatory response, and its activation has been significantly correlated with interleukin-6 and TNF-α production [17]. It is bound in cytoplasma to IκBα, which is phosphorylated by protein kinases stimulated by ROS. The release of NF-κB from IκB drives NF-κB to the nucleus (translocation) and binds to the promoter regions of inflammatory cytokines [18]. However, recognition by the IκBα gene of a sequence in the promoter gene of NF-κB may stimulate the latter's synthesis, which is followed by its entrance into the nucleus to bind and transport the activated NF-κB back to the cytoplasma. This art of feedback regulation is unique, representing as it does a limited factor of the inflammatory process since, when it is blocked, a synchronized increase of expression of multi-proinflammatory genes, such as cytokines and adhesion molecules, has been observed [19]. Following this, adhesion molecules may recruit neutrophils and T lymphocytes from the periphery to the site of inflammation, which, by producing the cytokines IL-1b, TNF-α and IL-6, further stimulate NF-κB, the result being amplification of the disease [19, 20]. Therefore, the proinflammatory cytokines, which activate and are activated by NF-κB, mediate the acute phase reaction that is epitomized by a dramatic increase of C-reactive protein (CRP) secretion from the liver [21]. The NF-κB activation cascade in inflammation is presented in ○ **Fig. 1**.

Selenium and Inflammation

There is good evidence that Se may have an impact on the course and outcome of a number of etiologically inflammatory diseases. Although the data come almost exclusively from in vitro studies, there is strong indication that viral, bacterial, or stress induced inflammation may be variably influenced by Se availability.

Decreased serum Se levels have been observed in acute and chronic inflammatory states with high CRP values [22]. Low Se levels have also been noted in severe inflammatory response syndrome (SIRS), which is marked by increased production of reactive oxygen species (ROS) by activated macrophages, induction of oxidative damage and tissue injury [23]. In critically ill patients, especially those afflicted by sepsis, low Se levels have been found and have been associated with more extensive tissue damage and organ failure. The values were even further decreased during the patients' stay in the ICU and correlated with increased ICU mortality [24]. By contrast, in a small observational study Se supplementation resulted in increased activity of GPx, reduced oxidative damage and improved clinical outcome [25]. In a randomized, multicenter study, Se administration reduced mortality in patients with severe sepsis and septic shock [26]. Moreover, in patients with severe burn injuries or traumas, also characterized by decreased Se levels and GPx activity, Se supplementation led to significant reduction in the secondary infection rate [27]. In all these studies a beneficial effect of Se supplementation on multiple organ function and outcome together with a clear tendency of improvement in mortality rates was registered. In contrast, in a randomized, placebo-controlled study conducted in patients with sepsis, continuous infusions of high doses (4 mg/1st day followed by 1 mg/day) of sodium selenite, although showing no toxicity, failed to improve the clinical outcome of the patients [28]. The discrepancies could be due to the different protocols of treatment between the stud-

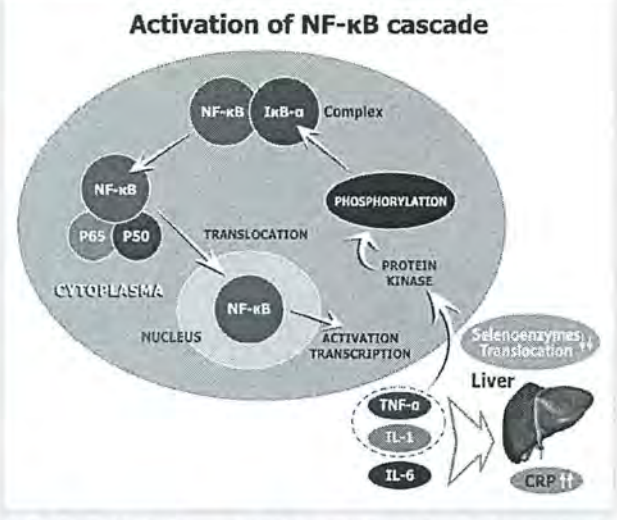

Fig. 1 The NF-κB-IκBα complex is located in cytoplasma of unstimulated cells. The IκBα is phosphorylated and degraded releasing the heterodimer NF-κBα, which is composed of various subunits of which p65 and p50 are the most common. NF-κB enters into the nucleus and transactivates genes of proinflammatory cytokines. TNF-α targets the liver, synchronized with IL-6, and releases of CRP, while IL-1, together with TNF-α, reactivates NF-κB by stimulating phosphorylation of IκBα by means of protein kinases. All inflammatory diseases may activate NF-κB by producing reactive oxygen species.

ies, including different doses of selenium and mode of application such as short- or continuous infusions.

Recently, the values of serum Se, CRP, and of lipid parameters were evaluated in gestational diabetic pregnant women and compared to those of control pregnant and nonpregnant women [29]. Serum Se levels were found lower in the diabetic and nondiabetic pregnant women and significant negative correlations were found between serum Se and CRP, total- and LDL-cholesterol values. According to the authors, these results indicate that low Se levels may be a predictor of lipid peroxidation. In a cross-sectional study in the region of Augsburg in Germany, using data from the monitoring of trends and determinants in cardiovascular disease, the intake of certain vitamins and Se resulted in lower CRP levels in women, indicating that certain micronutrients may influence the inflammatory response underlying the atherosclerotic process [30].

In celiac disease (CD), an intestinal inflammatory syndrome, malabsorption-induced selenium deficiency may propagate by modulating SeP genes expression and intestinal mucosal damage and may additionally predispose to complications such as AIT [28]. The overexpression of interleukin-15 (IL-15) in CD increases T helper 1 cytokine production, such as IFN-γ and TNF-α, and enhances intraepithelial lymphocytes cytotoxicity by protecting them from apoptosis [30]. Since IL-15 has also been found increased in AIT, Se has been recommended as a therapeutic measure in CD to block IL-15 in order to decrease epithelial damage and prevent such complications as AIT [31, 32].

In a recent prospectively conducted cohort study, a correlation was detected between mortality and morbidity among children born to HIV-infected mothers and Se deficiency [33]. SeP thioredoxin reductase 1 (TR1) was shown to negatively regulate the activity of Tat, the HIV-1 encoded transcriptional activator; consequently, increasing TR1 expression by Se supplementation may be a valid adjuvant therapy for HIV patients [34]. It has recently been suggested that Se may play a strong protective role in the diffusion pattern of HIV/AIDS patients [35], the hypothesis being that the antioxidant defense system driven by GPx constitutes an initial defense line against viral infection: this theory may explain the fact that HIV rarely infects individuals with high levels of Se and amino acids. Although there is no sound evidence at present to show that Se effectively reduces morbidity or mortality among HIV-infected patients, it is reasonable to follow the current WHO recommendations to promote adequate micronutrients intake, including that of Se, in these patients [36]. However, in a randomized, double-blind, placebo controlled study of Se supplementation in HIV-infected pregnant women in Tanzania, no improvement of disease progression or pregnancy outcome was achieved, although an apparent improvement in child survival has been reported [37]. Nevertheless, results of ongoing selenium trials are urgently awaited to elucidate the impact of Se on HIV-transmission endpoints.

Another trial investigated whether micronutrient supplementation and Se have any influence on treatment outcome in patients with tuberculosis (Tb) in Tanzania, a Se deficient area. A decrease in the spread of Tb, a reduced incidence of neuropathy and of genital ulcers, and a significant increase in CD3+ and CD4+ cell counts were documented [38]. These results lend support to Se and micronutrients supplementation in patients undergoing Tb chemotherapy.

The Mechanism of Action

The role of Se as an anti-inflammatory element is linked to its effect on immune cells and especially on the macrophage signal transduction pathways. A recent study revealed that Se supplementation results in a significant decrease in the bacterial endotoxin lipopolysaccharide (LPS) induced expression of the main proinflammatory genes TNF-α and cyclooxygenase-2 (COX-2) by inhibiting the MAP kinase pathways [39]. On the other hand, the increased TNF-α may induce maximum activation of NF-κB at suppressed Se levels while also increasing the secretion of CRP by the hepatocytes. TNF-α is a powerful inducer of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin), which are required in promoting endothelial cell proinflammation by recruiting leukocytes across the endothelium [40]. In this context, NF-κB is indispensable for the transcription of the adhesion molecule genes. In an in vitro study using human umbilical vein endothelial cells (HUVECS), added Se, in the form of sodium selenite, was able, in a dose dependent manner, to significantly inhibit TNF-α induced expression of the adhesion molecules [41]. Therefore, elevated Se levels may inhibit NF-κB via GPx and attenuate inflammation. Recently, a time-dependent increase in 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) production, whose formation is mainly mediated by cyclooxygenase-1 (COX-1), via selenium supplemented macrophages stimulated by LPS, has been described [42]. This might be an adaptive response for redox regulation and cell protection against proinflammatory gene expression.

In vivo, the level of Se regulates that of GPx, which tune intracellular ROS. Overexpressed GPx decreases ROS levels by inhibiting IκB-α phosphorylation and consequently the translocation of NF-κB. It has been reported that GPx can double IκB-α half-life and preserve its degradation [43]. Therefore, increased Se levels impede the transactivation of genes that encode inflammatory cytokines, thus inhibiting the acute phase protein release [44].

It has also been hypothesized that dietary Se may affect the metabolism of arachidonic acid and its enzymatic oxidation product, the eicosanoids [45]. Eicosanoids have been linked to the activation of phospholipase D (PLD), which plays a crucial role in the signal transduction in various cell types [46]. Lymphocytes from Se deficient rats produce significantly lower prostaglandins (PGs) than Se supplemented rats, conducing to decreased activation of PLD, lower generation of phosphatidic acid and diacylglycerol, and consequently to lower activation of protein kinase C (PKC) [47]. The addition of PGs can reverse these results and enhance PLD activity. Thus, dietary Se status may modify lymphocyte proliferation and immune response by altering the metabolism of arachidonic acid and the formation of eicosanoids.

Another important anti-inflammatory mechanism of selenium is mediated by its role in monocyte adhesion to endothelial cells and migration toward tissues. We know that monocytes adhere to endothelium and differentiate into macrophages, which are the main effectors of innate immunity in inflammation [48]. The monocytes adhesion to the endothelial cells is modulated by L-selectin, a member of the selectin family, which facilitates neutrophil migration during inflammatory response mediated by various ligands. L-Selectin expression can be markedly downregulated by metalloproteinases which, by cleaving its receptor, generate a soluble L-selectin that may

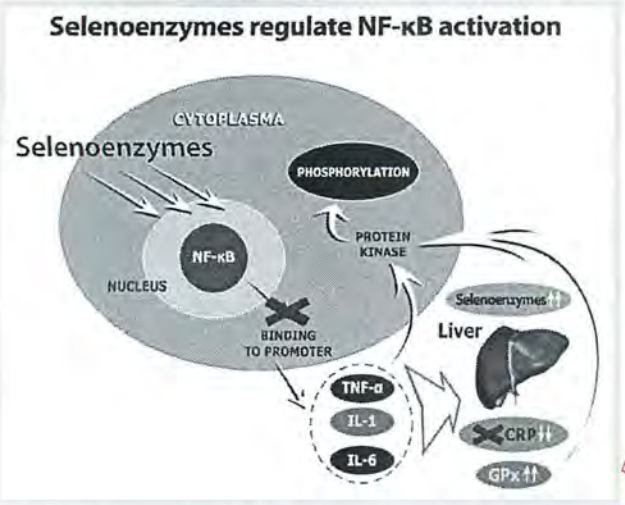

Fig. 2 The increase of CRP is conditioned by a marked reduction, up to 70%, of hepatic and serum selenium. Selenium supplementation leads to inhibition of NF-κB binding to the promoter genes, attenuation of cytokines release and consequently suppression of CRP synthesis. The activity of selenoenzymes is directly dependent on the plasma selenium levels. The increase of GPx inhibits, via reduction of hydrogen peroxide, the activation of protein kinases/phosphorylation of IκBα process.

inhibit the adhesion of lymphocytes to endothelial cells [49]. Although the biological role of sL-selectin has not been clarified, decreased levels have been associated with increased mortality in patients with SIRS [50]. Recently released data reported that Se was found to induce shedding of L-selectin from monocytes, leading to reduced differentiation into macrophages, while sL-selectin was considerably increased [51]. Though the pathophysiological significance of these findings has not been revealed, they may represent a valid underlying mechanism by which Se exerts its anti-inflammatory action in patients with sepsis.

It is also of interest that high doses of Se may impair other types of immunity such as antiparasitic or allergic asthma responses, indicating that the levels of Se may differently affect various types of immune response [52]. Although many molecular details have recently been elucidated, the picture is as yet far from complete. A schematic presentation of Se anti-inflammatory mechanisms is presented in ○ **Fig. 2**.

Chronic inflammation is influenced by genetic and environmental factors. Recently, interest has been focused on the role of selenoprotein S (SePS) in stress response and inflammation control. Functional analysis of SePS polymorphism, −105G A, significantly impairs SePS expression, which is followed by increased plasma levels of the cytokines IL-6, IL-1β and TNF-α [53]. These results provide good evidence of a link between SePS and cytokine production. On the other hand, even more recent data has failed to document any role of SePS polymorphisms in the susceptibility to develop immune-mediated diseases [54].

In conclusion, there is good evidence that Se, via variable and complex mechanisms, modulates the inflammatory response. There is therefore an urgent need for randomized, controlled studies, with a significant number of patients in order to provide statistical adequacy, so as to determine the mechanisms of action and the various types of immune responses before broad Se supplementation in patients with severe inflammatory diseases may be implemented.

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