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REVIEW

Selenium involvement in mitochondrial function in thyroid disorders

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Abstract
Selenium (Se), an important oligoelement, is a component of the antioxidant system. Over the last decade, it has been ever more frequently discussed in the context of thyroid disorders. Graves' disease and Hashimoto's thyroiditis, differentiated thyroid cancer, and even endemic goiter may have common triggers that are activated by excess reactive oxygen species (ROS), which are involved in various stages of the pathogenesis of thyroid disorders. Most oxidative events occur in mitochondria, organelles that contain enzymes with Se as a cofactor. Mitochondria are responsible for the production of ATP in the cell and are also a major site of ROS production. Thyroid hormone status (the thyroid being the organ with the highest concentration of Se in the body) has a profound impact on mitochondria biogenesis. In this review, we focus on the role of Se in mitochondrial function in thyroid disorders with impaired oxidative stress, since both thyroid hormone synthesis and thyroid dysfunction involve ROS. The role of Se deficiency or its excess in relation to mitochondrial dysfunction in the context of thyroid disorders is therefore of interest.

Keywords Selenium · Thyroid · Mitochondria · Oxidative stress · ROS

Introduction

Selenium (Se), an important oligoelement with essential biological functions, is a component of the antioxidant system. Over the last decade, it has been ever more frequently discussed in the context of thyroid disorders. Graves' disease (GD) and Hashimoto's thyroiditis (HT), differentiated thyroid cancer, and even endemic goiter have common triggers that are activated in the presence of excess reactive oxygen species (ROS), which are involved in various stages of the pathogenesis of thyroid disorders. ROS are free radicals or reactive metabolites and include superoxide (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide radical (NO), hydroxyl radical ($OH^·$), and singlet oxygen ($^1O_2$) [1]. Cellular ROS are produced by the mitochondrial respiratory chain and also by enzyme-catalyzed reactions involving NADPH oxidases, nitric oxide synthase (NOS), xanthine oxidase, lipoxygenase, cyclooxygenase, and cytochrome P450 enzymes [2].

In this review, we focus on the role of Se in mitochondrial function in thyroid disorders with impaired oxidative stress, since both thyroid hormone synthesis and thyroid dysfunction involve ROS. It is well established that most oxidative events occur in mitochondria, organelles that contain enzymes, and where Se acts as a cofactor. Thus, the role of Se deficiency or its excess in relation to mitochondrial dysfunction in the context of thyroid disorders is particular of interest.

Selenoproteins

Dietary Se is consumed mostly in its organic forms, namely, selenomethionine, selenocysteine, and selenocystathionine, or in the inorganic forms, selenite SeO_3^{2-} and selenide Se^{2-} [3]. Selenocysteine, which is first decomposed into selenide, is absorbed through dietary intake, selenoprotein degradation, or trans-selenation pathways. Selenide is used to synthesize selenocysteine-bound tRNA, the form that can be incorporated into selenoproteins [4]. The cotranslational insertion of selenocysteine into selenoproteins is controlled by a rate-limiting factor, known as selenocysteine insertion sequence

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(SECIS)-binding protein (SBP2), which is inhibited by inflammatory cytokines or mutations in the SECIS BP2 gene [5].

The 25 selenoproteins so far identified in humans, which are produced in the liver and exert actions in the kidney and other tissues, mainly have a role in antioxidant functions [6]. Se metabolism is controlled by hepatocytes that synthesize transporter selenoprotein P (SELENOP): SELENOP, accounting for the majority of circulating Se, is thus a good biomarker of Se status in humans [7]. Selenoproteins form part of a network of signaling molecules, including the steroid hormone vitamin D. The specific Se pool includes plasma selenoproteins (selenocysteine), such as SELENOP and glutathioneperoxidase (GPX3), while the nonspecific Se pool is bound to albumin (selenomethionine). Many isoforms of glutathioneperoxidase (GPX 1, 2, 3, 4, and 6), iodothyronine deiodinases (DIO 1, 2, and 3), selenoproteins, and thioredoxin reductases include Se as a prosthetic group with activity in cellular redox systems, acting in a tissue-specific manner [8, 9]. DIOs contain Se in the form of selenocysteine in the thyroid and other tissues [8].

The thyroid is the organ with the greatest abundance of Se, i.e., up to 1000 ng/g of the tissue, while, by comparison, fat tissue has only 120 ng/g, similarly to muscle, lungs, heart, and brain [10]. Se is vital for a wide range of biological processes; hence, Se homeostasis is essential for human health and well-being [3].

ROS in thyroid function

Reactive oxygen species (ROS) regulate cellular functions through redox-dependent mechanisms, including proliferation, differentiation, hormone synthesis, and stress defense response [11]. In the thyroid, several ROS are generated during iodine organification, essentially following the reactivity of hydrogen peroxide [12]. H_2O_2 is generated by the thyroid-specific NADPH dual oxidases (DUOX) 1 and 2, mostly by DUOX2, which are located in the thyrocyte apical membrane, together with their maturation factors, DUOXA 1 and 2. H_2O_2 generation is necessary for iodine organification, catalyzed by thyroperoxidase (TPO) in the colloid space and regulated by thioredoxin peroxidase, a stress- and iodine-induced protein, possessing strong redox activities [13]. The thyroid is protected from the harmful effects of ROS mainly by the antioxidant enzymatic system, which comprises superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), thioredoxin reductase (TRX), and peroxiredoxins (PRXs) [14]. In vitro, thyrocytes have shown higher survival rates after H_2O_2 exposure and the ability to rapidly degrade extracellular H_2O_2 as compared with other cell types; H_2O_2 upregulates GPx activity only in thyrocytes [15].

ROS neutralization is conducted primarily by the antioxidant enzymatic system (AES) through antioxidant trace elements (cofactors), such as Se, copper, manganese, and zinc. The "first line" enzymatic antioxidant defense system is composed of the superoxide dismutase (SOD) and catalase (CAT). When this mechanism is saturated, Se activates the "second line" through GPxs and TRx reductase [16]. Se protects the thyroid cells from oxidative stress, i.e., destruction by peroxides/radicals generated during thyroid hormone synthesis, through its antioxidative and anti-inflammatory effects [3]. Thyroid dysfunction is closely related to the deleterious effects of ROS, associated with severe thyroid epithelial cell inflammation and oxidative damage [16]. Females' higher susceptibility to thyroid disease is due to a sexual dimorphism in the intrathyroidal oxidative process. Indicatively, the thyroid of adult female rats exhibits higher H_2O_2 production and lower enzymatic antioxidant defense in comparison with males, an effect probably mediated by 17β-estradiol through DUOX enzymes [11].

Normal mitochondrial function and Se

The primary function of mitochondria is to supply energy by producing adenosine triphosphate (ATP) via the oxidative phosphorylation (OXPHOS) system, which consists of five mitochondrial complexes inserted in the inner mitochondrial membrane, the first four composing the electron transport chain. Impairment of OXPHOS causes mitochondrial diseases, a heterogeneous group of diseases that may affect any tissue in adults and children [17]. Nicotinamide adeninedinucleotide (NADH) and flavin adeninedinucleotide (FADH2) are used as electron donors by the first and second complex [18]. Mitochondrial function depends on the availability of reduced NADH and FADH2, proton donors generated during the utilization of fatty acids, glucose, and, to a smaller extent, amino acids [14]. The energy released is used to pump protons (H^+) from the mitochondrial matrix into the intermembrane space, leading to a proton gradient across this membrane. The energy stored is then used by the FOF1-ATPase (complex V) to generate ATP from ADP and inorganic phosphate [19].

Apart from energy metabolism, mitochondria play essential roles in cell signaling, cellular differentiation, and cell death, as well as in the regulation of the cell cycle and cell growth [20]. Mitochondrial dysfunction is involved in inflammatory and catabolic response, oxidative stress, insulin resistance and hyperglycemia, loss of muscle mass and function, and energy and protein deficit during and after critical illness [2, 21].

Mitochondria are constantly producing ROS, largely by means of single-electron reductions that leak from the electron transport chain [22], counteracted by the array of highly effective antioxidant enzymes present in the mitochondrial matrix. Under normal conditions, mitochondrial ROS production and removal are tightly balanced. A slight shift of the balance can

lead to the activation of important cell signaling pathways [22]. When ROS production significantly exceeds the capacity of the cellular antioxidant systems, oxidative stress occurs, inducing apoptosis through irreversible damage to the lipid mitochondrial membrane, enzymes, and mitochondrial DNA (mtDNA) [23]. Stress-mediated damage to mtDNA can result in a vicious cycle of ROS production (ROS-induced ROS release mechanism) and further mtDNA impairment, ultimately leading to loss of function of the enzymes in the electron transfer system and/or cell death [24], known as the "mitochondrial catastrophe" hypothesis [23].

Thyroid hormones, especially T3, are important regulators of mitochondrial quality-control mechanisms, acting either indirectly, through membrane-initiated pathways, or directly, by binding to specific thyroid hormone receptors in the mitochondrial matrix and stimulating transcription of the mitochondrial genome [25]. T3 diminishes excessive mitochondrial ROS production and oxidative stress through the following pathways:

- Activation of the AKT/eNOS axis (protein kinase B/nitric oxide synthetase), leading to increased transcription of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), which induces glutathione peroxidase (Gpx) and superoxide dismutase (SOD) [26]
- Transcriptional regulation of mitochondrial transcription factor A (Tfam)
- Inhibition of microARN-31,-155, and -222 [27] and activation of the mitochondrial K-ATP protective channel [28]

T3 also inhibits cellular inflammation induced by ROS and by the degraded mitochondria, stimulates the repair of misfolded proteins and damaged mtDNA, activates the clearance of degraded mitochondria (autophagy), and stimulates mitochondrial biogenesis [25]; these mechanisms have been demonstrated in various cell types (e.g., cardiac, neuronal, skeletal muscle, liver, and brown adipose tissue) [25, 29, 30].

Se is involved in cell bioenergetics thorough mitochondrial biogenesis. Se stimulates transcription factors, such as PGC-1α and nuclear respiratory factor 1, which are critical for mitochondrial biogenesis [31]. Se deficiency impairs mitochondrial biogenesis through decreased activity of DIOs [32].

Se and mitochondrial dysfunction in euthyroid sick syndrome

Mitochondrial dysfunction is associated with decreased energy production reflected by lower ATP availability and increased lactate levels. Meanwhile, Se preserves mitochondrial function and attenuates ischemia-activated autophagy [31]. In vitro studies in hippocampal cells have suggested that pretreatment with Se reduces the effect of hypoxia on mitochondrial complexes, effects which may be associated with modulation of Akt and the cAMP response element binding (CREB) protein [19].

Many severe chronic conditions are associated with imbalance in thyroid hormone metabolism in the absence of any primary thyroid disorder: sepsis, kidney or liver failure, malignancy, trauma, and severe nutritional deficit. This condition is called euthyroid sick syndrome, of which the most common findings are low T3 levels and increased reverse T3, while, in some severe cases, low T4 levels may also be encountered [33].

Se availability changes during critical illness. Circulating SELENOP declines in sepsis, thereby causing low Se levels. Dysregulation of the hepatic selenoenzyme DIO1 most probably contributes to the low T3 syndrome observed in severe diseases [34]. In critical illness with transient Se deficiency, Se is preferentially preserved for thyroid function [35]. Lower Se status is associated with worse clinical outcomes in sepsis patients (new organ failure, mortality) [19]. Se supplementation in critically ill patients with non-thyroidal illness improved morbidity but had no direct effect on free or total thyroid hormones [36]. A meta-analysis of 21 randomized controlled trials (RCTs) revealed that high-dose intravenous Se as monotherapy in critically ill patients had no effect on mortality [37]. In the elderly, reduced peripheral conversion of T4 to T3 with a lower T3/T4 ratio and overt hypothyroidism is frequently observed, this being related to impaired Se status [38].

ROS in autoimmune thyroid disease

Experimental studies in nonobese diabetic NOD.H2h4 mice which spontaneously develop thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) suggest that thyroid accumulation of ROS contributes to the initiation and progression of autoimmune thyroiditis. All cellular events with ROS production impact upon mitochondrial function. Low dietary Se potentiates the development of TPOAb and TgAb in NOD.H2h4 female mice [39].

Several susceptibility genes and selenoprotein gene polymorphisms are associated with thyroid autoimmunity, as described by GWAS in humans [40]. Accumulation of ROS has been shown to promote cleavage of thyroglobulin into several fragments, likely exposing the immune system to novel epitopes and thus enhancing the autoimmune response [41]. It is hypothesized that H_2O_2 leaks from the colloid of the damaged thyrocytes, thus creating a gradient along which leukocytes may be efficiently recruited [42]. Se is involved in T cell functioning, T-helper 1 (TH1) to T-helper 2 (TH2) ratio, and macrophage function, the latter demonstrating its complex role in immune regulation [43].

There are a few studies of ROS and oxidative stress in patients with Hashimoto's thyroiditis (HT). Comparing 93 patients with HT (divided into euthyroid, subclinical

hypothyroidism, and overt hypothyroidism subgroups) and 31 healthy controls, Ates et al. showed that serum oxidative stress parameters were higher in HT patients than in controls, particularly in overt hypothyroidism [44]. Baser et al. demonstrated that serum oxidant status was higher in 35 euthyroid HT patients than in 35 healthy controls and that it positively correlated with the levels of TgAb [45]. Ruggieri et al. analyzed in two studies several oxidative stress markers, including advanced glycation end products, in euthyroid HT cases and healthy controls. Oxidative stress was higher in HT patients, while TPOAb were the main predictor of oxidative status independent of thyroid function [46]. In humans, an increased prevalence of HT was reported in low-Se regions (reviewed in [9]).

GD is a complex autoimmune disease. Briefly, the loss of tolerance of T cells to the TSH-receptor and, as more recently discovered, to the IGF1-receptor [47], activates the autoimmune processes leading to hyperthyroidism and Graves' ophthalmopathy (GO). Mechanisms promoting oxidative stress have been implicated in the pathogenesis of GD. Hyperthyroidism increases production of ROS by elevated intracellular ATP consumption, increased oxygen consumption in most tissues and oxidative phosphorylation, and expression of adrenergic receptors, while it decreases antioxidants leading to oxidative stress [48].

The adverse effects induced by ROS have been suggested as being partly responsible for tissue injury [49]. Experimental studies in hyperthyroidism have documented enhanced activity of the TRx and GPx systems, stimulated by the calcium phosphatidylinositol cascade, which is usually activated in hyperthyroidism [50]. In humans, most studies have shown an increase in some of the antioxidant enzymes, either in plasma or in the erythrocytes [16, 48, 51], but with contradictory results regarding serum total antioxidant activity, which was, in fact, decreased in several studies, compared with controls [16, 51]. In a group of untreated hyperthyroid, hypothyroid, and control patients, respectively, the highest level of oxidative stress was recorded in hyperthyroid patients [16]. Treatment with thiamazole was shown to restore ROS and antioxidant activity indices [51]. Kocak et al. suggest that propylthiouracyl is more effective in decreasing oxidative stress markers in GD patients when compared with methimazole treatment [52].

Ongoing autoimmunity may contribute to increased oxidative stress even in euthyroid GD patients, while patients who have relapsed have increased levels of markers of oxidative stress [53]. In GO, the content of 8-hydroxy 2′-deoxyguanosine (8-OHdG), an important biomarker of oxidative DNA damage, was found to be significantly higher in orbital fibroblasts, together with O_2^- and H_2O_2, underscoring the major role that ROS play in the pathogenesis of GO [54]. 8-OHdG levels were also higher in the tears of GO patients, notably in patients with active disease, and correlated with the clinical activity score [55].

In addition, cigarette smoking, a well-known risk factor for GO [56], is a major source of ROS, which stimulate the NF-κB pathway, thus diminishing the effect of the corticosteroid treatment for GO. Se inhibits NF-κB from binding to gene promoters and, consequently, diminishes the production of the proinflammatory cytokines which stimulate the orbital fibroblasts [57]. ROS, such as H_2O_2, may also induce expression of high levels of cyclooxygenase (COX)-2; this reaction depends on the severity of GO in orbital fibroadipose tissues [58].

Se and cancer

While increased production of ROS and oxidative stress are demonstrated to favor the development of cancer, normal levels are necessary to eliminate the damaged cells from the body and to ensure normal immunity [59]. On the other hand, ROS can also induce cell senescence and apoptosis, thus playing an anti-tumorigenic role [4]. Se may exert antineoplastic activity via several potential mechanisms, including induction of apoptosis, antioxidation, alteration in DNA methylation status of tumor suppressor genes, cell cycle arrest, and stimulation of the immune system, as well as through its anti-inflammatory and antiangiogenic properties. Studies with a Se nanoparticle (Nano-Se) [60] have shown that the cellular apoptosis that it induced was associated with induction of mitochondrial membrane potential depolarization, release of cytochrome c to cytosol from mitochondria, and activation of caspases-9 and -3, and that it activated the Akt/ Mdm2/AR pathway [61].

Se compounds may have either antioxidant or pro-oxidant properties depending on their concentrations in both natural and experimental conditions [62]. Oxidative status differs according to the type of cancer, the stage of the disease, and other parameters. Experimental studies demonstrated that Se compounds have anticancer effects as pro-oxidants, although cancer cells also have a pro-oxidant status [63]. The effects of Se on cancer cells are highly concentration-dependent, low to moderate levels possibly stimulating growth in cell lines, whereas higher levels are cytotoxic [64].

Conclusion

Se is an essential component of the antioxidant defense system, acting at the mitochondrial level in numerous tissues. Though Se supplementation as adjuvant therapy to standard thyroid medication may be widespread, as shown in recent surveys [65], a growing number of studies report inconsistent results. Genetic factors, including single-nucleotide polymorphisms in the selenoprotein genes or in central genes implicated in Se metabolism or control of selenoprotein expression, may affect the relationship between Se status and health risks.

The available evidence from trials does not support routine Se supplementation in the standard treatment of patients with HT or GD (except for mild GO), nor in thyroid cancer. However, correction of moderate to severe Se deficiency might offer benefits in the prevention and treatment of these disorders. Further randomized controlled studies might reveal whether an individual Se dose adaptation to the degree of Se deficit, oxidative stress level, and genotype particularities may increase the therapeutic index and prevent undesirable toxicity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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