DOI 10.1002/mnfr.201100766 *Mol. Nutr. Food Res.* 2012, *56*, 1106–1121

REVIEW

Impact of dietary selenium intake on cardiac health: Experimental approaches and human studies

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Received: November 18, 2011
Revised: January 10, 2012
Accepted: February 3, 2012

Selenium, a dietary trace mineral, essential for humans and animals, exerts its effects mainly through its incorporation into selenoproteins. Adequate selenium intake is needed to maximize the activity of selenoproteins, among which glutathione peroxidases have been shown to play a major role in cellular defense against oxidative stress initiated by excess reactive oxygen species. In humans, a low selenium status has been linked to increased risk of various diseases, including heart disease. The main objective of this review is to present current knowledge on the role of selenium in cardiac health. Experimental studies have shown that selenium may exert protective effects on cardiac tissue in animal models involving oxidative stress. Because of the narrow safety margin of this mineral, most interventional studies in humans have reported inconsistent findings. Major determinants of selenium status in humans are not well understood and several nondietary factors might be associated with reduced selenium status. In this review, we discuss recent studies regarding the role of selenoproteins in the cardiovascular system, the effect of dietary intake on selenium status, the impact of selenium status on cardiac health, and the cellular mechanisms that can be involved in the physiological and toxic effects of selenium.

Keywords:
Cardioprotection / Heart / Oxidative stress / Selenium / Selenoproteins

1 Introduction

It is now well recognized that a dyshomeostasis of several microminerals might contribute to the development and outcome of cardiovascular diseases (CVD) [1]. Among these minerals, Selenium, a trace element with a strong bioactivity and a narrow safety margin, is of major importance to human health. Selenium was discovered by Berzelius in 1818. This Swedish chemist was asked to investigate toxic reactions in workers at a sulfuric acid plant in Gripsholm (Sweden). He suggested that contamination with arsenic was involved. After a few investigations, he concluded that a new chemical element was involved, which he called selenium, after Selene, the Greek goddess of the moon. In humans as well as in livestock, a spontaneous or experimental low selenium status has been suggested to be associated with increased risk of various pathologies, including CVD.

Based on both antioxidant properties of selenium due to its implication in glutathione peroxidase (GPx) [2, 3] and the strong inverse correlation between its serum concentration and coronary heart disease in humans [4], this mineral has raised considerable expectations for the prevention of CVD. Since the initial description of GPx-1 as the first selenium containing enzyme [2, 3], many selenoproteins have been identified, providing a wide panel of potential biomarkers of selenium status [5]. Recently, the characterization of the mammalian selenoproteome has confirmed that selenium is incorporated in the protein backbone as a selenocysteine. Several mechanisms have been suggested to mediate the biological effects of selenium. These

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Abbreviations: AP-1, activator protein-1; **APC**, anaphase promoting complex; **Bcl-2**, B-cell lymphoma-2; **Bcl-xL**, B-cell lymphoma-extra large; **b.wt.**, body weight; **CVD**, cardiovascular disease; **Cx43**, connexin-43; **GJC**, gap junction; **GPx**, glutathione peroxidase; **GSH**, reduced glutathione; **GSSG**, oxidized glutathione; **NFκB**, nuclear factor kappa-B; **NHANES**, National Health and Nutrition Examination Survey; **PAK-1**, serine/threonine p21-activated kinase; **PP2A**, protein phosphatase 2; **RDA**, recommended dietary allowance; **ROS**, reactive oxygen species; **Sel S**, selenoprotein S; **TNF-α**, tumor necrosis factor-alpha; **TrxR**, thioredoxin reductase; **TUIL**, tolerable upper intake level; **TyrK**, tyrosine kinase; **TyrP**, tyrosine phosphatase

include cellular antioxidant defence systems, enzymatic cofactor, kinase regulation, gene expression, selenoprotein-dependent pathways, immune function, and inflammation.

Because of its potential cardioprotective activity, the effects of selenium on cardiovascular endpoints have been extensively studied in animal models of myocardial ischemia and reperfusion. However, although most of these experimental studies have evidenced highly cardioprotective effects of high selenium diets in animals, several interventional studies in humans have only reported inconsistent findings on the association between selenium supplementation and coronary risk.

The relationships between selenium dietary intake, selenium status, and cardiac health require additional experimental evidence to provide new insights into the role of selenium in human cardiac biology, to elucidate the underlying mechanisms linking selenium status to CVD endpoints, and to determine the causal effect of selenium on cardiovascular risk factors.

The main purposes of this article are to review recent studies on selenium dietary intake in humans as well as in different animal models, to evaluate the impact of various levels of dietary selenium intake (deficient intake, normal recommended or moderately supplemented diet, selenium overload) on cardiac function and resistance to oxidative stress, and finally to synthesize the most recent investigations on cellular mechanisms that might be involved in the effects of selenium on cardiovascular health.

2 Bioactive forms of selenium

Until the middle of the 20th century, selenium was considered a toxic mineral [6,7]. Its essential nature was incidentally demonstrated in the late 50s by Klaus Schwarz on an experimental model of liver necrosis in rats fed a *Saccharomyces cerevisiae*-based diet [8].

The interest on the role of selenium in animal nutrition began in the early 1960s when selenium supplementation was shown to prevent numerous diseases in farm animals [9]. Since that time, selenium has been shown to be at the active site of GPx [3, 10], and numerous selenoproteins have been identified in mammals.

Contrarily to most metals, selenium is not incorporated into proteins simply *via* ionic interactions but is a part of the backbone of the peptide. Indeed, in cysteine, the sulfur can be replaced by selenium leading to the formation of the 21st amino acid, selenocysteine [11]. After the initial description of the antioxidant effect of selenium via GPx by Rotruck et al. [3], Forstrom et al. [12] were the first to report the presence of a selenocysteine in GPx. A few years later, Low and Berry [13] confirmed that, in eukaryotic cells, the incorporation of selenocysteine was controlled by three untranslated regions of mRNAs, named the selenocysteine insertion sequence. This sequence is responsible for recoding the stop codon UGA in a selenocysteine codon.

To date, at least 25 selenoproteins have been identified in mammals (Table 1). The first classes initially described were the GPx isoforms, the thioredoxin reductases (TrxR), and the iodothyronine deionidases. This later subfamily of deionidases is involved in the activation and deactivation of thyroid hormones [19]. GPxs, TrxRs, and selenoprotein W are directly involved in the regulation of oxidative stress. Both GPxs and selenoprotein W are hydroperoxidases mainly involved in hydroperoxide detoxification by using glutathione as a cofactor. TrxRs catalyse the NADPH-dependent reduction of thioredoxin in cellular redox pathway regulation.

Another important selenoprotein initially described in rat plasma by Motsenbocker et al. [23] is selenoprotein P. This protein contains 10–30 selenocysteine residues and is secreted from liver cells. Selenoprotein P plays a major role in selenium homeostasis by acting as the main selenium carrier in the body [24]. Several of the most recently discovered selenoproteins probably also play a role in oxidative stress regulation. For example, selenoprotein H was shown to act as a transcription factor regulating both glutathione and GPx expression [29] and selenoproteins S and K have been suggested to be potentially related to inflammation [36, 37, 39].

Most of the other selenoproteins (for more details see Table 1) already described are proteins with largely unknown functions [5, 39].

3 Role of selenoproteins in the cardiovascular system

The most studied selenoproteins in the context of the cardiovascular system is the GPx family (Table 1). The use of nutritional models of animals receiving different levels of selenium [14,16,44–48], as well as experiments on GPx-knockout mice [49] have led to the conclusion that GPx activity is involved in oxidative stress limitation by detoxifying hydroperoxides. More recent studies also conferred to TrxR some regulatory functions in the cardiovascular system mainly through the induction of changes in redox status, leading to the oxidation of intra and intercellular signaling molecules [50] and impacting, in turn, on adaptive mechanisms such as ventricular remodeling [51].

Until now, few studies have examined the role of other selenoproteins in cardiovascular physiology and disease. Nevertheless, this area of research seems promising since a study by Lu et al. has demonstrated that selenoprotein K, an endoplasmic reticulum protein, contributes to antioxidant defence systems in isolated cardiomyocytes [40]. In addition, Hoffmann et al. have suggested that selenoprotein R, which is overexpressed in the myocardium during hypertrophy, may be involved in intracellular oxidative stress reduction [33].

Table 1. Selenoproteins in animal eukaryotic cells: A focus on cardiovascular physiology

	General physiology		Cardiovascular physiology		
	Ref.	Characteristics and/or physiological function	Effect of selenium intake modifications	Implication in cardiovascular system	Ref.
Glutathione peroxidase	[2]	Detoxification of hydroperoxides using GSH as a cofactor	Modification of cytosolic and mitochondrial activity	Protection against oxidative stress and/or ischemia-reperfusion	[14] [15] [16]
Thioredoxine reductase	[17]	Regulation of cellular redox pathways by reducing thioredoxin with NADPH	Modification of activity	Limitation of reperfusion-induced injuries	[18]
Iodothyronine deionidase	[19]	Cleavage of iodine–carbon bonds in thyroid hormone metabolism	Type-1 expression is modulated by Se in vascular wall	Type-2 overexpression associated with remodeling in dilated cardiomyopathy. Type-3 overexpression in hypertrophy and heart failure	[20] [21] [22]
Selenoprotein P	[23] [24]	High number of Sec. Implication in Se delivery/ homeostasis Potential antioxidant functions	Reduced expression in Se deficiency in endothelial cells	Undetermined	[25]
Selenoprotein W	[26]	Similar to GPx. Implication in white muscle disease	Cardiac overexpression by increased Se intake	Undetermined	[27] [28]
Selenoprotein H	[29]	Nuclear transcription factor that modulates GSH level and GPx activity	N/A	Expression in the nucleus of cardiomyocytes	[30]
Selenoprotein I	[31]	Ethanolamine transferase Phospholipid synthesis	N/A	Undetermined	
Selenoprotein R	[32]	Member of the methionine sulfoxide reductase family	N/A	Development of cardiac hypertrophy is associated with overexpression. Potential implication in intracellular oxidative stress reduction	[33]
Selenoprotein N	[34]	Localized in the ER membrane. Implication in muscle development (genetic deletion causes myopathy in humans)	N/A	Development of cardiac hypertrophy is associated with overexpression. No cardiac functional role indentified	[33] [35]
Selenoprotein S	[36] [37]	Removal of misfolded protein from the ER membrane	N/A	Variation in locus is associated with coronary heart disease and ischemic stroke	[38]

Table 1. Continued

	General physiology		Cardiovascular physiology		
	Ref.	Characteristics and/or physiological function	Effect of selenium intake modifications	Implication in cardiovascular system	Ref.
		Potential role in inflammation			
Selenoprotein 15	[39]	Small ER protein. Protein folding function	N/A	Undetermined	
Selenoprotein K	[39]	Small ER protein related to inflammation	N/A	Anti-oxidant function in cardiomyocytes for regulation of cellular redox balance	[40]
Selenoprotein M	[41]	Small ER protein with neuroprotective function. Implication in cytosolic calcium regulation	N/A	Undetermined	
Selenoprotein T	[42]	Small ER protein Potential implication in calcium homeostasis in neuroendocrine secretion	N/A	High level of expression in heart tissue	[43]
Selenoprotein O	[39]	Widely distributed	N/A	Undetermined	
Selenoprotein V	[39]	Expression limited to testes	N/A	Undetermined	

Ref., references; N/A, not available; Se, selenium; Sec, selenocystein; GSH, reduced glutathione; ER, endoplasmic reticulum.

4 Dietary selenium intake

4.1 Selenium intake in humans

Selenium can be found in numerous food sources including dairy products, vegetables, meat, fish, seafood, and nuts. The major chemical form of dietary selenium is selenomethionine, but other forms of selenium such as selenite can also be metabolized into biologically active methylated selenocompounds.

Selenium can also interact with several heavy metals such as mercury, arsenic or chromium, forming inert metal selenide complexes or modifying the kinetics and metabolism of these toxic elements [48, 52]. This phenomenon, which has been suspected to occur in fish or seafood from polluted areas, is probably beneficial since it may reduce the toxicity of the contaminants. Nevertheless, this binding may reduce the bioavailability of selenium and therefore reduce the ability of selenium from this food to increase selenium status [53].

The content of selenium in food depends on the selenium content of the soil where plants are grown or animals are raised. For example, soils in the high plains of Northern Nebraska and South Dakota have very high levels of selenium. People as well as cattle living in these regions generally have the highest selenium intakes in the United States [54]. In the US, food distribution patterns across the country help prevent people living in low-selenium geographic areas from having low dietary selenium intakes. In contrast, selenium deficiency has been reported in humans in some parts of China or in the center of Europe where soils have very low amounts of selenium, because most food in these areas are grown and eaten locally.

In humans, the threshold for selenium deficiency is about 0.3 to 0.4 microgram per kg body weight and per day (μg/kg b.wt./day). On the opposite, the tolerable upper intake level (TUIL) of selenium above which toxicity is observed is around 8–15 μg/kg b.wt./day (Fig. 1A) but most expert panels consider prudent to limit the intake of selenium from all sources, to 5–6 μg/kg b.wt./day [53].

The recommended dietary allowance (RDA) for selenium is 55 μg/day for adults [55], which corresponds to 0.5–1.0 μg/kg b.wt./day (Fig. 1A). This value has been determined as the intake believed to be necessary to maximize the activity of GPx in plasma. Indeed, GPx, as well as all other selenoproteins except selenoprotein P, reaches a plateau of maximal activity at plasma-selenium levels between 70–90 μg/L. Further increase in selenium status leads to

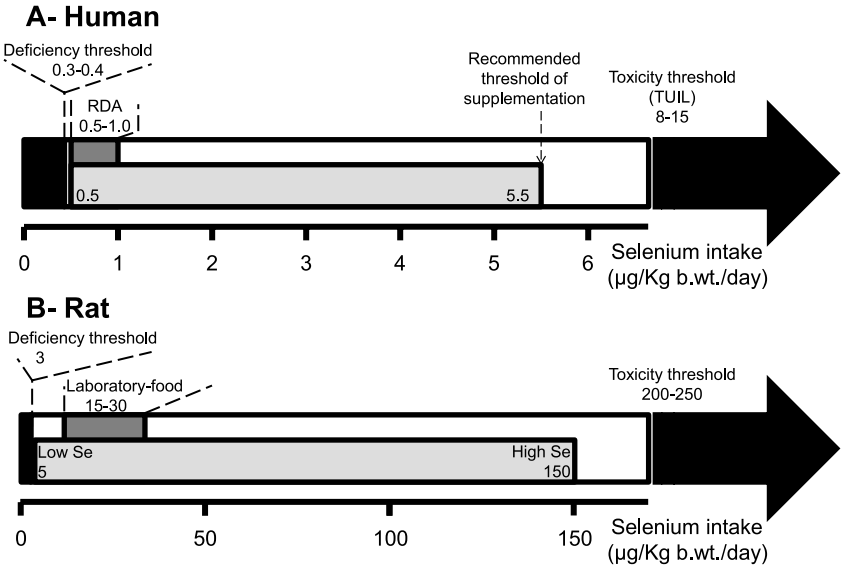

Figure 1. Dietary selenium intake in humans (A) and in rats (B). Selenium intake is expressed as microgram/kg body weight/day (µg/kg b.wt./day). RDA: recommended dietary allowance; TUIL: tolerable upper intake level.

Table 2. Plasma selenium contents in different mammalian species

Models	Plasma Se (ng/mL)	References
Human	80–120	[58] [59] [60]
Swine	100	[61]
Sheep	275	[27]
Ewes	140–200	[62] [63]
Lambs	80	[62]
Rabbit	150	[64]
Rat	300–600	[18] [65] [66] [67]

nonspecific incorporation of selenomethionine into albumin and other proteins, without increasing the antioxidant status [56].

Finally, it has been suggested that optimal selenium intake for any individual is likely to depend on selenoprotein gene polymorphisms that may affect the risk of disease [57].

4.2 Selenium intake in animal models

From two centuries ago, selenium toxicity was recognized in various animal species [6, 7, 9]. After 1957, with the discovery that selenium was an essential trace mineral [8], nutritionists started extensive studies to figure out the biological and biochemical functions of this essential element.

There is a large variability of plasma-selenium content among mammalian species (Table 2). This variability could be related to differences among species in intestinal selenium uptake, integration into selenoproteins, and nonspecific integration of selenomethionine into other proteins. Nevertheless, the pathological phenotypes that are related to selenium deficiency or selenium overload are conserved among species. For this reason, to date, the vast majority of experimental studies on the physiological effects of dietary selenium intake are conducted in rodents.

According to the literature, the threshold for selenium deficiency in rats can be evaluated as being about 3 µg/kg b.wt./day, and the toxicity threshold close to 200 µg/kg b.wt./day (Fig. 1B). The most commonly used standard commercial diets for rodents contain 150–300 µg selenium per kg food, depending on the origin of the cereals constituting the basis of the diets. The use of such diets allows a dietary selenium intake of 15–30 µg/kg b.wt./day, i.e. 30 times more than the RDA in men (Fig. 1).

5 Impact of selenium intake on the heart

It is now well admitted that systematically increasing selenium intake in human populations is not necessarily beneficial, although these interventions are limited to populations with low or moderately low dietary selenium intake. As a consequence, interest in determining the maximum dose of selenium that may be safely ingested chronically has recently increased.

Although both animal and human studies have evidenced inverse associations between selenium status and CVD [18, 68], results from a recent observational study [69] has suggested a possible U-shaped association between selenium status and CVD risk.

In the following sections, the impact of selenium deficiency, optimal selenium intake, and selenium overload on the cardiovascular system are discussed. Particular emphasis is given to how selenium is linked to redox signaling and oxidative stress in myocardial cells under both physiological and pathophysiological conditions (Table 3).

Table 3. Levels of selenium intake in experimental animal models and implication in cardiovascular physiology

Ref.	Animal experimental design			Cardiovascular evaluation		
	Selenium intake[a)]	Model	Estimated selenium intake[b)] (μg/day/animal)		Biomarkers of cardiac Se status	Effects on cardiovascular system (High Se versus Low Se)
[18]	5 weeks Low: 0.05 High: 1.50	Rat	Low: 1 High: 30	In vivo regional ischemia/reperfusion	GPx TrxR	Limitation of postinfarction remodeling. Limitation of TNF-α expression
[70]	8 weeks Low: 0.05 High: 1.50	Rat	Low: 1 High: 30	Ex vivo ischemia/reperfusion	GPx	Limitation of Cx43 dephosphorylation
[16]	10 weeks Low: 0.05 High: 1.50	Rat	Low: 1 High: 30	In vivo myocardial infarction	GPx GSH/GSSG	Limitation of developed pressure alteration. Limitation of infarct size
[71]	10 weeks Low: 0.05 High: 1.50	Senescent rat	Low: 1 High: 30	Ex vivo ischemia/reperfusion	[Se] GPx	Preservation of postischemic cardiac function. Limitation of ultrastructural damage
[15]	10 weeks Low: 0.05 High: 1.50	Rat	Low: 1 High: 30	Ex vivo regional ischemia/reperfusion	GPx	Limitation of reperfusion -induced arrhythmias
[72]	10 weeks Deficient: 0.01 Control: 0.16	Rat	Deficient: 0.2 Control: 3.2	Ex vivo ischemia/reperfusion	GPx	Improvement of myocardial functional recovery. Limitation ultrastructural damage
[14]	8 weeks High: 2.50	Rat	Control: N/A High: 50	Ex vivo doxorubicin exposure	GPx	Limitation of deleterious effects of adriamycin
[73]	10 weeks Low: 0.11 Control: 0.24 High: 2.40	Rat	Low: 2.2 Control: 4.8 High: 48	Ex vivo ischemia/reperfusion	GPx	Limitation of functional and ultrastructural damages
[74]	3 weeks 50 μg/kg i.p.	Rat	Control: N/A High: 17	Oxidative stress induced by doxorubicin	TrxR	Limitation of doxorubicin-induced left ventricular dysfunction
[75]	5 weeks 0.00; 0.05; 0.24; 1.00	Rat	From 0 to 20	Ex vivo ischemia/reperfusion	GPx TrxR	Increased sensitivity in deficient rat
[76]	5 weeks 0.00; 0.05; 1.00	Rat	From 0 to 20	Ex vivo ischemia/reperfusion	GPx TrxR	Limitation of protein oxidation and lipid peroxidation
[77]	High: 2 mg/L drinking water	Pregnant female rat		Ex vivo isolated heart from 10-day-old rats	Blood Se content	Limitation of reperfusion-induced alterations
[48]	High: 0.50	Female rat	Control: N/A High: 10	In vivo chromium-induced cardiotoxicity	GSH level GPx	Limitation of oxidative stress markers
[47]	Deficiency: 0.00 Low: 0.50 High: 1.00	SHR rat	Deficiency: 0 Low: 1.5 High: 30	In vivo hypertension and heart failure	GPx TrxR	Limitation of oxidative stress damage and mortality
[78]	4 weeks 1.16 mg/L drinking water	Cocaine-treated rats		Myocardial function	GPx	Limitation of cocain-induced cardiac dysfunction and oxidative stress
[79]	4 weeks 0.3 mg/kg/day i.p.	Diabetic rats	Control: N/A High: 60	Myocardial function	N/A	Limitation of diabetes-induced cardiac dysfunction

Ref, references; N/A, not available; [Se], cardiac selenium concentration.
a) If not indicated, the unit of selenium intake is: mg/kg of diet.
b) These values have been evaluated from food selenium content, age, and weight of the animals used (when available).

5.1 Effect of selenium deficiency

5.1.1 Keshan's disease and infectious myocarditis

Keshan's disease is probably the most studied human disease related to selenium deficiency [80]. This dilated cardiomyopathy, which mainly developed in children from the Keshan province of the People Republic of China, is characterized by multifocal myocardial necrosis and calcification, and is often reversible after selenium supplementation [80]. Nevertheless, although selenium deficiency appears to be a primary pathogenetic factor in the occurrence of this disease, it is currently rather considered as a conditional predisposing factor than an etiologic factor for the juvenile cardiomyopathy. Indeed, in addition to its well-documented geographical distribution, Keshan's disease also exhibits a pronounced seasonal variation that has led the Chinese researchers to suspect the role of an infectious agent [81]. In 1980, Bai et al. [82] published their first results on selenium-deficient mice, showing that selenium supplementation decreases the cardiotoxicity of the coxsackie B_4 virus, a virus that was isolated from Keshan's disease victims. A few years later, the same group [83] reported that a strain of mice naturally resistant to viral-induced myocarditis becomes susceptible when fed a selenium-deficient diet. Finally, in a recent study, Jun et al. [84] have demonstrated, in a mice model with deficient selenium dietary intake, an increase in coxsackie virus-induced myocarditis.

The implication of the antioxidant properties of selenium through GPx activity in the development of this increased sensitivity to the viral infection was evidenced in studies using genetically modified mice models. For instance, Beck et al. [85] have shown that 50% of GPx-1 knockout mice ($GPx^{-/-}$) developed myocarditis when infected with the virus, whereas wild-type mice were resistant. Interestingly, as in Keshan's disease, selenoproteins are suspected to play a major role in the cardiac consequences of another infectious disease named Chagas disease. Chagas disease is a tropical parasitic disease cause by the protozoan *Trypanosoma cruzi*. It has been shown that a low selenium status increases heart dysfunction in patients infected with the parasite [86].

5.1.2 Cardiovascular disease

Experimental studies on the effects of selenium deficiency on CVD without infectious origin were focused on GPx activity, considering that cardiovascular pathologies that are associated with low selenium intake are mainly related to increased oxidative stress (Table 3). In this context, Venardos et al. [76] have reported an increased myocardial protein and lipid oxidation after a sequence of ischemia-reperfusion in a rat model of selenium deficiency. Our group had previously demonstrated that a selenium-deficient diet in rats exacerbated the alteration of cardiac functional recovery after ischemia-reperfusion and increased the ultrastructural damage to the myocardium [72]. These consequences of low dietary selenium intake were associated with a significant alteration of GPx activity in blood as well as in myocardial cells [72].

5.1.3 Cardiotoxicity of doxorubicin

The role of selenium has also been studied in another situation of cardiac oxidative stress: the cardiotoxicity of doxorubicin (Table 3). Doxorubicin is an anthracycline antibiotic used in cancer chemotherapy. It is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft-tissue sarcomas. Doxorubicin's most serious adverse effect is life-threatening heart damage. Numerous studies on doxorubicin have demonstrated that oxidative stress plays a pivotal role in doxorubicin's cardiotoxicity [87]. Generation of oxidative stress by doxorubicin can be explained on the basis of its chemical structure. The quinine containing tetracyclic moiety of doxorubicin can be reduced into a semiquinone by addition of a single electron. This electron can be transferred from the semiquinone to an oxygen molecule, leading to the formation of a superoxide anion radical. The latter interacts with surrounding molecules leading to cardiomyocyte injury and cardiomyopathy [88].

Several studies have tried to check whether selenium, due to its antioxidant properties, might exert a beneficial effect against doxorubicin toxicity. In this context, two main groups of studies have been carried out, a first one with those related to selenium deficiency in rats and a second one with the effects of selenium supplementation in several experimental models [89]. Most authors [44, 49, 90–92], but not all [93, 94], reported that selenium as well as GPx-1 deficiencies lead to an increased doxorubicin cardiotoxicity in rats. These studies mainly concluded that lipid peroxidation, or free radical generation, was involved in the toxic effects occurring in the selenium deficient rats, which through several direct or indirect mechanisms (DNA oxidative damage, mitochondrial alterations, etc.) affected the final degree of the cardiotoxic insult.

5.2 Recommended intake and moderate selenium supplementation

5.2.1 High versus low selenium intakes

Several experimental studies have been conducted in rats in order to investigate the cardiac effects of selenium supply within the physiological range from 3 to 200 μg/kg b.wt./day (Fig. 1B, Table 3). Most of these studies have compared groups of animals with very low selenium intake, just above the deficiency threshold, to groups receiving high levels of selenium. In this context, Venardos et al. [76] have demonstrated that selenium supply with 1 mg Se/kg food

(i.e. 70–100 μg/kg b.wt./day) for 5 weeks reduces protein oxidation and lipid peroxidation consecutive to myocardial ischemia-reperfusion compared with animals fed a low-selenium diet containing 0.05 mg Se/kg food (i.e. 3.5–5 μg/kg b.wt./day). Under similar conditions of selenium supply (i.e. low selenium: 3.5–5 μg/kg b.wt./day versus high selenium: 100–150 μg/kg b.wt./day), our group has described, on both in vivo and in vitro models of cardiac ischemia and reperfusion, improved recovery of cardiac function [16], reduced myocardial infarct size [16, 18] and reduced incidence of reperfusion-induced ventricular arrhythmias [15, 70] in rats with the highest selenium intake.

In addition to these effects on ischemia-reperfusion, high selenium intake reduces cardiovascular toxicity of doxorubicin by protecting cardiac function and ultrastructure [14, 74, 87].

5.2.2 Saturable cardioprotective effect of selenium

Studies in which intermediate selenium intakes were provided to rats have demonstrated that cardiac sensitivity to ischemia and reperfusion decreases from selenium supplies just above the deficiency threshold up to values of 12–20 μg/kg b.wt./day and then reaches a plateau that is maintained up to the threshold for selenium toxicity [73, 75, 76]. This concept (Fig. 2) is particularly relevant in the context of basic studies on cardiac pathophysiology, since the variability of selenium content in commonly used standard laboratory diets (Fig. 1B) might have a significant impact on the experimental results.

Similarly, in humans, an interesting study by Hawkes et al. [95] provides arguments in favor of the saturable benefit of selenium supply and points out the lack of beneficial effects of selenium supplementation in populations with adequate intake. Indeed, these authors have demonstrated that, in healthy North American subjects with normal plasma-selenium level (140-150 μg/L), an additional selenium intake beyond the nutritional requirement (300 μg/day per os for 48 weeks) does not confer any significant improvement of endothelial function. Thus, on the basis of such epidemiological evidence, it can be concluded that selenium level predicts cardiovascular risk in populations with lower selenium status but is not associated with risk in populations with higher selenium status [96]. Thus, the effect of selenium on cardiovascular health appears to be saturable.

5.3 High selenium intake and selenium overload

5.3.1 General aspects

Selenium toxicity can occur with acute or chronic ingestion of excess selenium. Symptoms of acute selenium intoxication in humans include nausea, vomiting, nail discoloration, hair loss, fatigue, and orthostatic hypotension [97]. To our knowledge no experimental study is currently available on the direct cardiac effects of selenium overload. However there is growing epidemiological evidence for several associated side effects of high selenium intake that might impact cardiovascular health. Moreover, recent studies [60, 98–100] have shown that very moderate increases in selenium status, far below the doses inducing intoxication symptoms, can increase cardiometabolic risk factors such as type 2 diabetes or dyslipidemia in populations with normal selenium intake.

5.3.2 High selenium intake and diabetes

Since the initial discovery by Stranges et al. [101] that selenium supplementation (200 μg/day) increases the risk of type 2 diabetes in subjects with high baseline plasma selenium, several epidemiological studies have raised additional concerns about the association of selenium intake above the RDA with diabetes risk. As an example, the SELECT study that was initially designed to assess the prevention of cancer by oral selenium and vitamin E in North America was prematurely stopped, not only because of the lack of efficacy of selenium supplementation (from L-selenomethionine; 200 μg/day, per os) in cancer prevention but because of a small, not statistically significant increased risk of type 2 diabetes in participants taking selenium alone [102]. In addition, Stranges et al. [103] have recently reported that in a population of North Italian women with normal average selenium intake (55.7 μg/day), increased dietary selenium intake was associated with an increased risk of type 2 diabetes. The mechanisms underlying this adverse effect of high selenium intake are not yet elucidated. Nevertheless, a loss of insulin responsiveness in isolated soleus muscle strips exposed to selenate or selenite was reported more than 15 years ago [102].

5.3.3 High selenium intake and dyslipidemia

From the results of different NHANES (National Health and Nutrition Examination Survey) analyses, it can be concluded that higher plasma selenium levels are associated with adverse lipid profiles, including higher total cholesterol and triglyceride levels [100, 103].

Similarly, other studies in Europe have reported an association between high selenium exposure and an adverse lipid profile. In the double-blind randomized, placebo-controlled primary prevention trial SUVIMAX designed to test the effect of long-term antioxidant supplementation in reducing ischemic CVD and cancer, Hercberg et al. [104] have reported a positive association between selenium level and total cholesterol at baseline. In addition, several studies have reported an association between selenium supplementation and a higher level of triglyceride [104], a lower level of HDL cholesterol [104] or an increased level of LDL cholesterol [105].

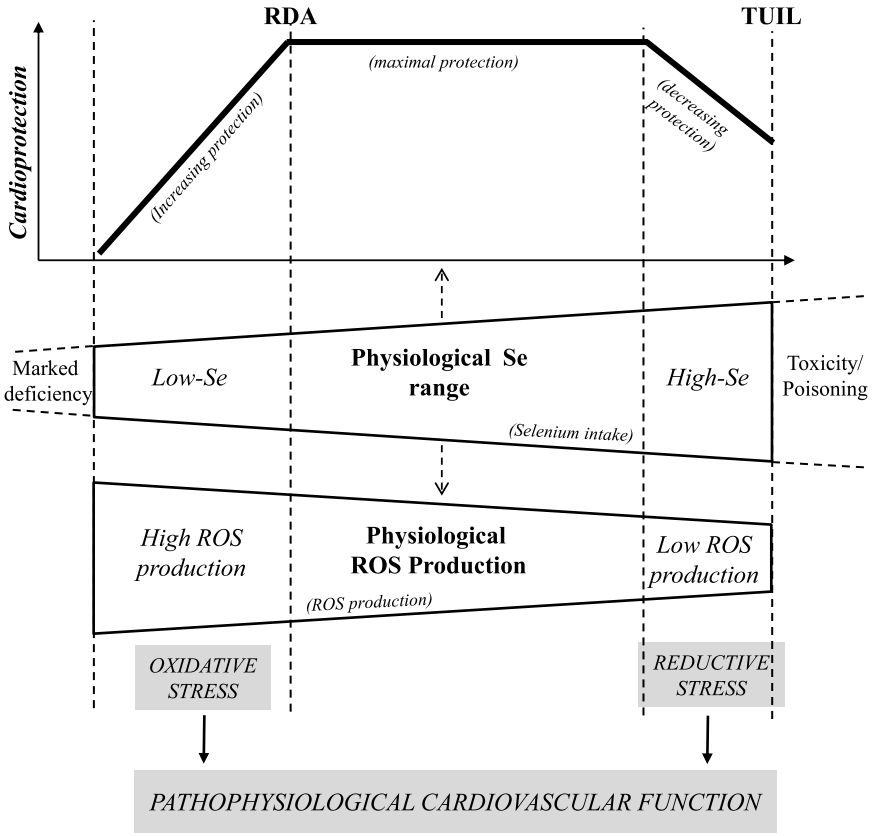

Figure 2. Effects of selenium, within the range of tolerable intake, on cardiac resistance to oxidative stress. For low selenium intakes, cardiac resistance to oxidative stress increases with selenium intake and reaches a plateau at the value of RDA. For supranutritional selenium intakes below the TUIL, increased selenoprotein expression affects physiological redox signaling and causes a reductive stress. Se: selenium; RDA: recommended dietary allowance; TUIL: tolerable upper intake level.

5.3.4 High selenium intake and arterial hypertension

Because oxidative stress is involved in the development of hypertension [106], it has been suggested that diverse nutritional factors affecting antioxidant status may be involved in the regulation of blood pressure and the prevention of hypertension [107]. The few studies that have evaluated the association between blood selenium and arterial blood pressure in humans have reported contradictory results [105, 108–112]. Nevertheless, at the phase of recruitment of the noninterventional EVA (Etude sur le Vieillissement Artériel) study, men with hypertension, but not women, had higher serum selenium concentrations compared to those without CVD or risk factors [105]. More recently, in a crosssectional analysis of 2638 North American subjects >40 years old who participated in the 2003 to 2004 NHANES, Laclaustra et al. [112] have reported that high serum selenium concentrations were associated with higher prevalence of hypertension.

6 Mechanisms of action of selenium

6.1 Cardioprotective action of selenium

The currently proposed pathways for the beneficial effects of selenium on cardiac health are presented on Fig. 3.

6.1.1 Increased antioxidant status

It is now widely admitted that excessive reactive oxygen species (ROS) production plays a major role in the pathogenesis of CVD such as ischemic heart disease and heart failure. When production of ROS overwhelms the capacity of endogenous antioxidant defenses, oxidative stress develops, causing harmful effects to the myocardium, including contractile failure and ultrastructural alteration [113]. Trace elements, such as selenium, mainly prevent ROS-induced cell damage by increasing antioxidant enzyme activities [73]. Indeed, adequate selenium intake or moderate selenium supplementation helps optimizing GPx and TrxR activities, as well as GSH/GSSG ratio (Table 3). It is commonly admitted that its ability to modulate cellular antioxidant status plays a pivotal role in the cardioprotective mechanisms of selenium (Fig. 3).

6.1.2 Reduced apoptosis

To our knowledge, to date no study has evaluated the impact of selenium intake on myocardial cell apoptosis. Experimental studies that have been performed on other cell types have reported very heterogeneous results, ranging from anti [126–128] to proapoptotic [129, 130] effects of selenium. Nevertheless, a nutritional study in rats, by Mukherjee et al. [116],

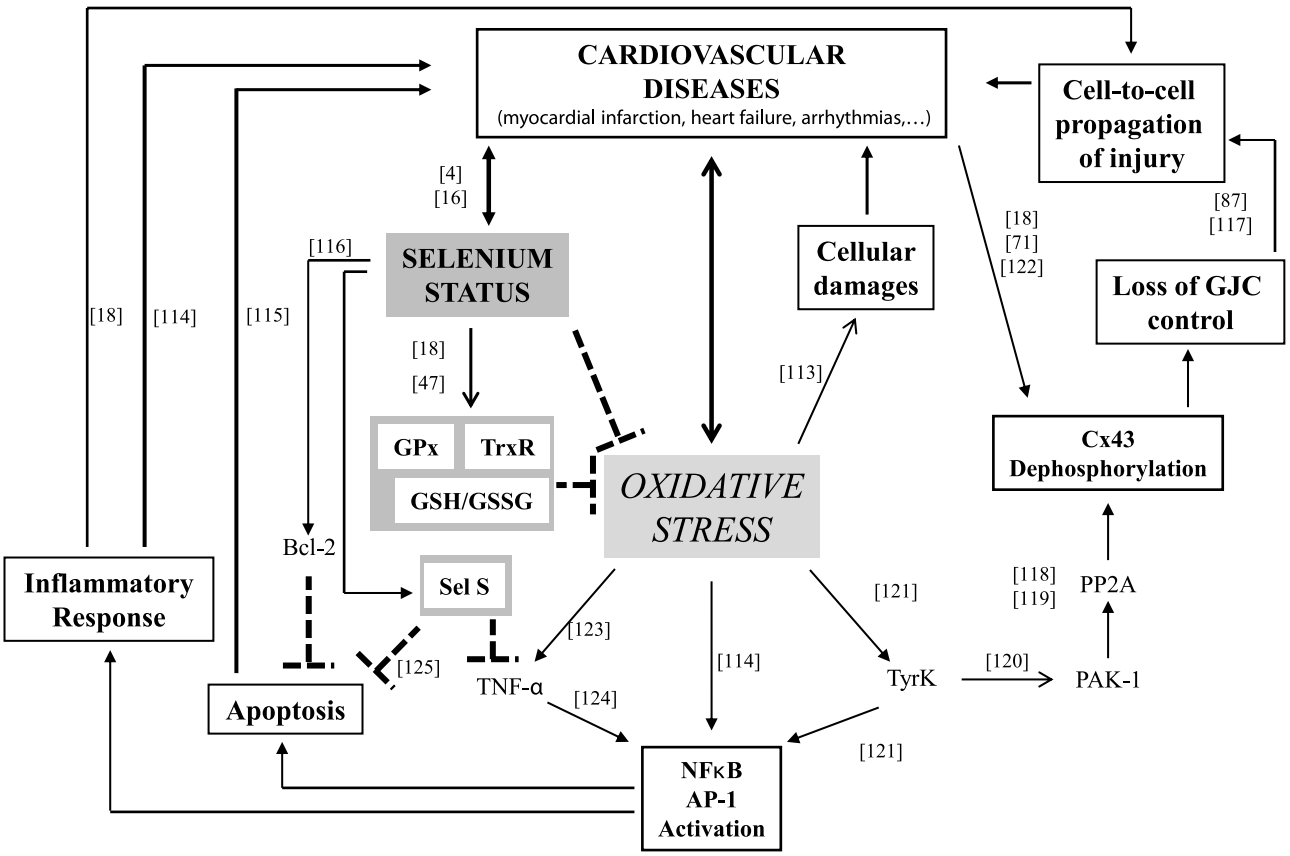

Figure 3. Cardioprotective effects of physiological intake of selenium. Sel S: selenoprotein S; GPx: glutathione peroxidase; TrxR: thioredoxin reductase; Bcl-2: B-cell lymphoma-2; GSH/GSSG: reduced/oxidized glutathione ratio; NFkB: nuclear factor kappa-B; AP-1: activator protein-1; GJC: gap junction; Cx43: connexin-43; TyrK: tyrosine kinase; PAK-1: serine/threonine p21-activated kinase; PP2A: protein phosphatase 2.

has demonstrated that broccoli consumption triggers cardioprotection against ischemia and reperfusion by generating an antiapoptotic signal through activation of several survival proteins such as Akt and Bcl-2 (Fig. 3). Because broccoli contains high amounts of selenium, it can be reasonably suggested that this cardioprotective effect was related, at least in part, to this micronutrient. Another argument in favor of an antiapoptotic effect of selenium was provided by animal studies on different models of selenoprotein suppression. A study by Crack et al. [131] on GPx-1-knockout mice has shown that GPx-1 expression plays an important regulatory role in the protection of neural cells against ischemia-reperfusion-induced apoptosis. In addition, selenoprotein S gene expression has been shown to be activated by an ischemic stress in astrocytes, and suppression of selenoprotein S expression by small interfering RNA severely increases astrocyte apoptosis during ischemia [125]. These results suggest that optimal selenoprotein expression is a key factor of the survival signal in situations of oxidative stress. Therefore, adequate selenium intake might be necessary to ensure adequate antiapoptotic systems.

6.1.3 Reduced alteration of the NFκB pathway

Increased activation of the transcription factor NFκB is usually associated with survival signals in cardiomyocytes as well as in other cell types. Nevertheless, prolonged and excessive ROS production can also lead to the activation of proinflammatory and proapoptotic pathways [132] through an imbalance between the tyrosine kinase (TyrK) and tyrosine phosphatase (TyrP) that regulate NFκB translocation [121] (Fig. 3). Therefore, excessive stimulation of NFκB in the myocardium during an ischemic episode, leads to increased cytokine production [133–135].

It has been recently demonstrated that selenium reduces the nuclear translocation of NFκB during myocardial infarction in rats [114]. In addition, increased selenium intake reduces cardiac infarct size and postischemic TNF-α production in a rat model of transient regional ischemia [18]. The precise mechanism of NFκB inhibition by increased selenium status remains unclear. Nevertheless, it has been suggested that this protective effect of selenium could be related to increased antioxidant status through GPx and TrxR activation [18]. In

addition, selenoprotein S could directly interact with the inflammatory process and therefore limit cytokine production [37, 38].

6.1.4 Reduced connexin-43 (Cx43) dephosphorylation

In addition to the altered activation of NFκB, the imbalance between TyrK and TyrP induced by excessive ROS production can also trigger Cx43 dephosphorylation (Fig. 3). Indeed, the increased TyrK activity increases p21-activated kinase (PAK-1) phosphorylation and in turn activates protein phosphatase 2 (PP2A), a phosphatase responsible for Cx43 dephosphorylation (Fig. 3) [118, 120]. Cx43, the major ventricular gap junction protein, is responsible for intercellular communication and electrical coupling of cardiomyocytes. Cx43 dephosphorylation, by increasing cell-to-cell communication, is a determinant of cell death progression and therefore impacts myocardial infarct size and cardiac remodeling after infarction [136, 137]. Selenium intake, within the range of physiological values, is able to modulate the dephosphorylation of Cx43 induced by experimental myocardial infarction in rats [18, 70]. In rats, high preischemic selenium intake (150 μg/kg b.wt./day) reduces Cx43 dephosphorylation [18, 70], limits reperfusion-induced arrhythmias [18], reduces infarct size [18, 70], and improves cardiac remodeling [18] compared with low preischemic selenium intake (5 μg/kg b.wt./day).

6.2 Cardiotoxicity of selenium

6.2.1 Subclinical metabolic toxicity of selenium

The increased risk of diabetes and dyslipidemia in randomized trials of selenium containing supplements has raised the possibility that selenium intake below the current TUIL (400 μg/day) may be harmful [138]. Nevertheless, the mechanisms underlying this subclinical metabolic toxicity of high selenium exposure and prolonged use of selenium supplementation remain unclear.

Interestingly, some studies have reported that an overexpression of GPx-1, as well as other antioxidant selenoproteins, induces insulin resistance and obesity through an alteration of physiological cellular redox signaling [139, 140]. It has therefore been suggested that excessive selenoprotein expression caused by supranutritional selenium intake may in turn cause metabolic disturbances by altering normal redox signaling (Fig. 2) [141].

6.2.2 Toxicity of selenium overload

Excess selenium accumulates as selenomethionine in proteins of different tissues including the heart [9, 16, 142]. The substitution of selenomethionine for methionine alters protein stability [143] and affects the thermodynamics of target protein binding of the calcium regulatory protein, calmodulin [144]. This phenomenon can impact calcium homeostasis in cardiomyocytes and therefore impair cardiac contraction and relaxation. In addition, selenium overload induces cellular apoptosis through activation of p53 [145], caspase-9, Bcl-xL, and APC [130].

Finally, at high concentrations, selenium is prooxidant. Indeed, both selenite and methylselenol can generate superoxide anions in presence of reduced glutathione. Both superoxide anions and depletion of intracellular pools of reduced glutathione contribute to selenium-induced oxidative stress [146, 147].

7 Conclusions

During the last two decades, many experimental and clinical studies on selenium have produced a great deal of evidence showing that this essential trace element is of major importance to human health and various diseases. In particular, it has been demonstrated that selenium is involved in several important metabolic pathways, including antioxidant cellular defense systems, functioning of the immune system, and production of active thyroid hormone. The health promoting properties of selenium have been related to biological functions of selenoproteins at the active site of which selenium is present as selenocysteine, the 21st amino acid. In addition, several selenoproteins have been described, among which GPx and TrxR enzymes have been the first to be characterized and are now recognized as functionally important owing to their antioxidant activity. Finally, it has been reported that adequate dietary selenium intake is needed to maximize the activity of GPxs and other selenoproteins. This review summarizes current knowledge on the recommended dietary selenium intake in humans as well as in experimental animals and describes the effects of selenium deficiency or selenium overload on cardiovascular health. The mechanisms of action of selenium on cardiac tissue submitted to pathophysiological conditions in which an excessive production of ROS occurs, such as ischemia-reperfusion or doxorubicin treatment, are summarized. The relationships between selenium intake, selenium status, and cardiovascular health, or risk of CVD, require clarification before dietary recommendations could be done in clinical practice. More research is still needed to improve our understanding of selenium requirements for optimal cardiovascular health.

The authors have declared no conflict of interest.

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