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Rapid Letter

Preischemic Selenium Status as a Major Determinant of Myocardial Infarct Size *In Vivo* in Rats

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ABSTRACT

Prospective epidemiological studies have shown that the incidence of numerous cardiovascular pathologies is correlated with body selenium status. However, it remains unclear whether selenium status also influences the outcome of myocardial infarction. The aim of the present study was to test whether dietary selenium intake affects myocardial necrosis induced by transient regional ischemia *in vivo* in rats. For this purpose, male Wistar rats received either a high-selenium (High-Se: 1.5 mg of Se/kg) or a low-selenium (Low-Se: 0.05 mg of Se/kg) diet for 10 weeks. Animals were subjected to 30 min of myocardial ischemia induced by coronary artery ligation followed by 60 min of reperfusion. Pre- and postischemic blood samples were collected for glutathione (GSH and GSSG) determination and for glutathione peroxidase (GSH-Px) assessment. Our results show that high-selenium intake reduces myocardial infarct size (High-Se: 25.16 ± 1.19% versus Low-Se: 36.51 ± 4.14%, $p < 0.05$), preserves postischemic GSH/GSSG ratio (High-Se: 1.37 ± 0.37 versus Low-Se: 0.47 ± 0.10, $p < 0.05$), increases plasma GSH-Px activity, and improves postischemic mean arterial pressure. In conclusion, preischemic body selenium status is a major determinant of the outcome of myocardial ischemia *in vivo* in rats probably because it influences the cellular redox status. *Antioxid. Redox Signal.* 6, 792–796.

INTRODUCTION

Selenium is a constituent of the enzyme glutathione peroxidase (Se-GSH-Px) (14). As Se-GSH-Px can reduce oxidative stress and limit platelet aggregation (16), high selenium status might theoretically be protective against cardiovascular disease (11). On this basis, for several decades, numerous experimental and epidemiological studies have attempted to determine whether body selenium status influences both the incidence and the severity/prognosis of cardiovascular disease.

The association between low selenium status and the incidence of ischemic heart disease was established more than 30 years ago for populations in areas such as Finland, where selenium intake was exceptionally low (15). However, several other studies, especially when carried out in North America, have not shown a clear relationship between cardiovascular risk and low selenium status (17, 21). The possible explanation for this discrepancy is that the influence of selenium on the incidence of ischemic heart diseases might only be relevant in populations with low selenium status, lower than the concentrations that are generally observed in the U.S.A., as well as in a large part of Europe (13).

As a matter of fact, selenium deficiency has been identified as a major factor in the etiology of certain nonischemic chronic heart failure syndromes, especially in very low-selenium soils such as eastern China (Keshan disease) and western Africa (7, 11). More recently, we have demonstrated

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that the severity of postischemic chronic heart failure in French patients, assessed by peak exercise oxygen consumption (VO_2), is strongly correlated with body selenium (NYHA functional class I or II) (2). The reference serum selenium concentration in normal French adults is 70–100 µg of selenium per liter of plasma, which is known to be sufficient to maximize the activity of the antioxidant Se-GSH-Px in plasma (range 89–114 µg/L) (4). This finding therefore supports the hypothesis that selenium status plays a role in the severity of chronic heart failure, even in human populations in areas where selenium intake is reasonably high.

Several experimental studies have shown either cardioprotective effects of increased selenium intake (1, 12, 18) or cardiotoxic effects of selenium deficiency (20) on isolated hearts subjected to ischemia–reperfusion. Nevertheless, these experiments were performed using extreme selenium intakes and therefore cannot be compared to cardiovascular pathologies in most human populations.

On this basis, the present study was designed to investigate the possible link between plasma selenium content and the outcome of myocardial ischemia in rats receiving a dietary selenium intake within the range of physiological values. Two groups of rats were therefore constituted, receiving either a moderately low-selenium diet (0.05 mg of Se/kg of food) or a moderately high-selenium diet (1.5 mg of Se/kg of food) for 10 weeks. At the end of the 10-week diet, rats were subjected to *in vivo* coronary artery ligation followed by reperfusion. Ischemia-induced impairment of the redox status and infarct size were assessed.

MATERIALS AND METHODS

Animals and diets

Male Wistar rats were randomly assigned to one of the two following experimental groups: a low-selenium group (Low-Se; $n = 10$), receiving a standard diet containing 0.05 mg of selenium/kg of food for 10 weeks, and a high-selenium group (High-Se; $n = 10$), receiving the same diet containing 1.5 mg of selenium/kg of food for 10 weeks. Selenium content in both diets was adjusted by sodium selenite (Sigma, Lyon, France) addition to a low selenium-containing basic-diet (18).

Rats were housed under conditions of constant temperature, humidity, and standard light/dark cycle (12 h/12 h). They had free access to tap water and food. They received human care in compliance with the guidelines formulated by the European Community for use of experimental animals (L358–86/609/EEC).

Diets were replaced every day, and body weights were determined weekly for the 10-week duration of the experiment.

In vivo myocardial ischemia–reperfusion

Ten weeks after the beginning of the diets, animals were anesthetized with sodium pentobarbital (60 mg/kg of body weight, i.p.) and anesthesia was maintained by a continuous intravenous infusion (5 µl/min/100 g) of sodium pentobarbital (6 mg/ml). Body temperature was kept constant at 37°C with a heating blanket controlled by a thermostat and connected to a rectal thermocouple (Homeothermic Blanket System, Harvard Apparatus Ltd., Edenbridge, U.K.). The animals were intubated through tracheotomy and mechanically ventilated (tidal volume: 0.8 ml/100 g of body weight; ventilation rate, 70 strokes/min). An SRP-407 Millar Mikro-Tip® catheter transducer was inserted into the ascending aorta through the right carotid artery to monitor arterial blood pressure, and a D2 electrocardiogram was monitored. A left thoracotomy was performed to allow access to the heart. A silk suture (5/0) was passed around the left coronary artery, and a small polyethylene catheter was used to form a snare. All rats were allowed 20 min after completion of the surgical preparation to reach steady state before the beginning of the protocol. The left coronary artery was occluded by pulling the snare for 30 min, and reperfusion was induced by releasing the snare for 60 min.

Postmortem studies

At the end of the surgical protocol, the heart was removed and cannulated via the aorta and perfused with 15–20 ml of saline at room temperature to wash out the blood. The left coronary branch was reoccluded, and 2 ml of Evans Blue saturated solution was perfused through the aorta. The risk zone was determined as the tissue area without blue dye. The heart was then briefly frozen in liquid nitrogen and stored at −20°C.

Hearts were cut into six to seven transverse slices of 1 mm in thickness each. Viable cells from the risk zone were stained by incubating the slices in triphenyltetrazolium chloride in sodium phosphate buffer (pH 7.4) at 37°C for 20 min. Finally, slices were immersed in 10% formalin for 4 days to enhance the contrast between stained and unstained areas (= infarct zone). Volumes of infarct, risk, and safe zones were calculated using NIH Image software (NIH AutoExtractor 1.62; National Institutes of Health, Bethesda, MD, U.S.A.). Risk zone was expressed as a percentage of total ventricular volume, and infarct size was expressed as a percentage of risk zone.

Glutathione and glutathione peroxidase (GSH-Px) assays

Blood samples were collected at the end of the stabilization period and at the end of reperfusion in five rats per group. Each blood sample was divided into two aliquots: 100 µl was immediately mixed with 10 µl of 1-methyl-2-vinylpyridinium trifluoromethanesulfonate, rapidly frozen, and kept at −80°C for oxidized glutathione (GSSG) measurement; another 100 µl was directly frozen and kept at −80°C for reduced glutathione (GSH) (50 µl) and GSH-Px activity (10 µl) measurements.

Glutathione assays were performed with the GSH/GSSG-412™ BIOXYTECH® kit (OXIS Health Products, Inc., Portland, OR, U.S.A.) according to the manufacturer's recommendations. GSH-Px activity was determined on crude preischemic samples by the modified method of Flohe and Günzler (5) using *tert*-butyl hydroperoxide as substrate.

Selenium assay

Plasma selenium content was evaluated by gas chromatography coupled to mass spectrometry technique as previously described by Ducros and Favier (3).

Statistical analysis

All results are expressed as means ± SEM and compared with a nonparametric Mann–Whitney *U* test. Intragroup comparisons were performed by a paired Student's *t* test. In all cases, the significance threshold was fixed at $p = 0.05$.

RESULTS

General aspects

During the 10-week diet, selenium intake did not affect the growth rate of the animals (Table 1). Total increase in body weight was similar in both experimental groups (Low-Se: 268 ± 5 g versus High-Se: 264 ± 5 g, NS, Table 1). However, as expected, a moderate (10%), but significant difference in plasma selenium concentration was found between groups at the end of the 10-week diet (Low-Se: 4.51 ± 0.10 µmol/L versus High-Se: 5.08 ± 0.13 µmol/L, $p < 0.01$, Table 1). Similarly, plasma GSH-Px was 17% higher in the High-Se group than in the Low-Se group (High-Se: 1,125.6 ± 40.7 g versus Low-Se: 964.4 ± 46.6 g, $p < 0.05$, Table 1).

Effect of selenium intake on aortic pressure (AP)

The evolution of AP during the surgical protocol is presented in Fig. 1. The level of selenium intake did not affect preischemic AP (Low-Se: 90.7 ± 6.9 mm Hg versus High-Se: 91.9 ± 6.1 mm Hg, NS) under our experimental conditions. Moreover, preischemic heart rate was equivalent in both experimental groups (Low-Se: 385 ± 10 beats/min versus High-Se: 401 ± 15 beats/min, NS).

During ischemia, the evolution of AP was similar in both groups with a rapid initial fall followed by a progressive recovery, which slowed to reach a peak value after 15–20 min of ischemia. This peak was then followed by a rapid deterioration of AP.

Postischemic recovery of AP was significantly improved in the High-Se group compared with Low-Se throughout reperfusion (after 60 min of reperfusion, Low-Se: 45.1 ± 5.4 mm Hg versus High-Se: 67.3 ± 4.6 mm Hg, $p < 0.01$).

TABLE 1. EFFECT OF THE 10-WEEK DIETS ON GROWTH RATE AND PLASMA SELENIUM STATUS

	Low-Se (n = 8)	*High-Se (n = 9)*
Body weight (g)		
Day 0	152 ± 4	149 ± 3
Day 70	420 ± 9	413 ± 8
Plasma Se status (µmol/L)	4.51 ± 0.10	5.08 ± 0.13*
Plasma GSH-Px activity (IU/L)	964.4 ± 46.6	1,125.6 ± 40.7†

Groups are defined in the text. Values are expressed as means ± SEM.

*$p < 0.01$; †$p < 0.05$, versus Low-Se (Mann–Whitney *U* test).

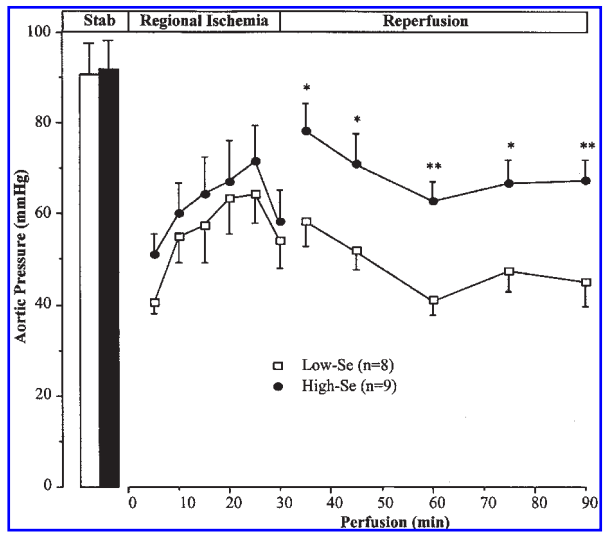

FIG. 1. Evolution of aortic pressure during stabilization (Stab), regional ischemia, and reperfusion in High-Se and Low-Se rats. Results are presented as means ± SEM (Mann-Whitney *U* test). *$p < 0.05$; **$p < 0.01$, versus Low-Se.

Effect of selenium intake on myocardial infarct size

As illustrated in Fig. 2A, myocardial risk zone, expressed as a percentage of total ventricular volume, was equivalent in both experimental groups (41.1 ± 1.8% versus 44.1 ± 1.9%, for Low-Se and High-Se rats, respectively; NS). As shown in Fig. 2B, infarct size was significantly ($p < 0.05$) higher in Low-Se (36.51 ± 4.14%) compared with High-Se rats (25.16 ± 1.19%).

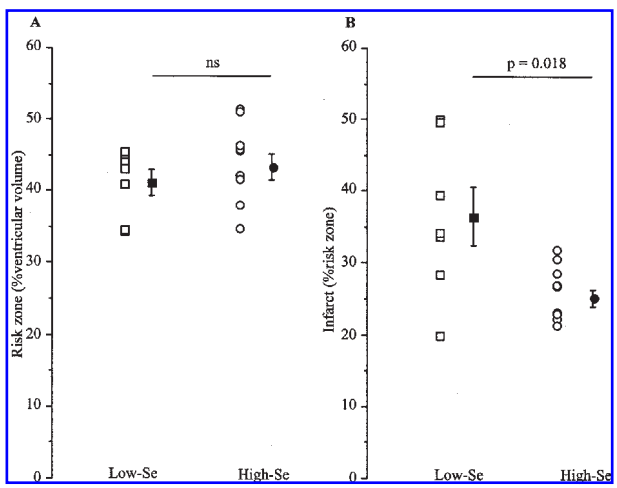

FIG. 2. Scatter plots of the (A) risk zone and (B) infarct size in High-Se (squares) and Low-Se (circles) rats. Risk zone is expressed as a percentage of total ventricular volume, and infarct size is expressed as a percentage of risk zone. Open symbols, individual data; closed symbols, means ± SEM (Mann–Whitney *U* test).

TABLE 2. EFFECT OF *IN VIVO* MYOCARDIAL ISCHEMIA–REPERFUSION ON PLASMA GLUTATHIONE IN HIGH-SE AND LOW-SE RATS

	GSH (μmol/L)	*GSSG (μmol/L)*	*GSH/GSSG*
Low-Se			
Preischemia	274.6 ± 22.7	180.5 ± 18.7	1.64 ± 0.31
Postischemia	120.2 ± 29.3*	253.1 ± 30.5	0.47 ± 0.10*
High-Se			
Preischemia	285.6 ± 57.5	192.7 ± 20.2	1.46 ± 0.26
Postischemia	260.8 ± 69.4	191.6 ± 5.9†	1.37 ± 0.37†

Groups are defined in the text. Values are expressed as means ± SEM ($n = 5$ per group).
*$p < 0.05$, versus preischemic value (paired Student's t test).
†$p < 0.05$ versus Low-Se (Mann–Whitney U test).

Effect of selenium intake on GSH/GSSG ratio

Plasma GSH/GSSG ratio was calculated for both experimental groups before (preischemia) and after the ischemia–reperfusion sequence (postischemia). As shown in Table 2, there is no difference in this ratio at the end of the stabilization period between the two experimental groups. However, ischemia induced a dramatic decrease (−71%) in the plasma GSH/GSSG ratio in the Low-Se group (1.64 ± 0.31 versus 0.47 ± 0.10, for preischemia and postischemia, respectively; $p < 0.05$), whereas this ratio remained almost unchanged (−6%) in the High-Se group (1.46 ± 0.26 versus 1.37 ± 0.37, for preischemia and postischemia, respectively; NS). This impairment of postischemic GSH/GSSG ratio in the Low-Se group was found to be due to both a significant decrease in plasma GSH ($p < 0.05$) and a nonsignificant increase in plasma GSSG (180.5 ± 18.7 versus 253.1 ± 30.5, for preischemia and postischemia, respectively; NS).

DISCUSSION

The main result of our study is that body selenium status influences the development of myocardial necrosis, as well as the recovery of AP early after ischemia–reperfusion in rats. Moreover, relatively mild differences in the level of selenium intake were shown to affect dramatically the redox status of the animals (assessed by the preservation of the GSH/GSSG ratio) during ischemia–reperfusion-induced oxidative stress.

There is compelling evidence for reactive oxygen species (ROS) formation and oxidative damage contributing to myocardial necrosis in the ischemic reperfused heart. Although the source of ROS during ischemia and reperfusion remains highly controversial, it is well established that ROS can attack the sarcolemmal phospholipids, initiating lipid peroxidation and forming cytotoxic lipid hydroperoxides that cause damage to the heart. The enzymatic defense against ROS injury is a two-step process. At first, superoxide anion is converted into hydrogen peroxide, and this is followed by detoxification of that hydrogen peroxide. The latter function is accomplished by two enzymes: catalase and GSH-Px. In the myocardium, catalase is present in relatively low amounts, and hydrogen peroxide removal depends mainly on GSH-Px activity. Numerous experimental studies using transgenic animals or transfected cells suggest that tissue GSH-Px activity is a crucial determinant of cardiac susceptibility to ischemia and reperfusion. As an example, Yoshida *et al.* (22) have been the first to demonstrate that hearts from GSH-Px-1 gene knockout mice develop a larger infarct after *ex vivo* transient regional ischemia than hearts from wild-type mice. In contrast, transgenic rat cardiomyocytes overexpressing GSH-Px have been shown to be more resistant to a sequence of hypoxia–reoxygenation than control nontransgenic cardiomyocytes (8).

In the present study, a lower susceptibility to myocardial ischemia–reperfusion was found in rats fed a high-selenium diet. The essential trace element selenium is an integral part of the enzyme GSH-Px. Therefore, dietary selenium intake is a major factor of GSH-Px cellular activity regulation. Consistently with our previous study (19), we have shown that our model of high-selenium diet leads to a 17% increase in cardiac GSH-Px activity when compared with the low-selenium diet. Therefore, the observed beneficial effect of the high-selenium intake on ischemia–reperfusion injury might be related, at least in part, to an increase in GSH-Px activity.

Central to the neutralization of hydrogen peroxide and lipid peroxides by GSH-Px is the cysteine-containing tripeptide GSH. Cardiac GSH deficiency intensifies myocardial ischemia–reperfusion injury (10), whereas treatment with exogenous GSH protects the heart against such injury (6). Generation of GSH from its oxidized form GSSG, allowing subsequent maintenance of intracellular GSH pools, is catalyzed by the enzyme glutathione reductase. The activity of glutathione reductase requires reducing equivalents in the form of the pyridine nucleotide NADPH. Although the importance of NADPH in the cardiac antioxidant systems is well established, the mechanisms responsible for generating NADPH during ischemia–reperfusion remain unknown (9). The present study shows that high selenium intake paradoxically preserves the GSH/GSSG ratio during the sequence of ischemia–reperfusion. This finding is unexpected because high selenium intake is associated with increased GSH-Px activity, which should increase GSSG production during an oxidative stress. We suggest that selenium intake might also regulate the mechanisms by which NADPH is generated, allowing the maintenance of the GSH level.

In conclusion, the present study shows for the first time that high preischemic selenium intake reduces myocardial infarct size *in vivo* in rats and that this beneficial effect might be related, at least in part, to cellular redox status preservation. Further studies are now requested to determine how

selenium promotes GSSG reduction and preserves the GSH/GSSG ratio during ischemia–reperfusion.

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ABBREVIATIONS

AP, aortic pressure; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; High-Se, high-selenium group; Low-Se, low-selenium group; ROS, reactive oxygen species; Se-GSH-Px, selenium-dependent GSH-Px.

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