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Original article

The effect of zinc and/or vitamin E supplementation on biochemical parameters of selenium-overdosed rats

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Abstract

The normotensive (Wistar) and spontaneously hypertensive (SHR) rats were examined to assess the response of the organism to selenium (Se) overdose. Moreover, the effect of zinc (Zn) and vitamin E, i.e. dietary components interacting in many biochemical processes with Se, on the Se uptake was evaluated. The control group was fed an untreated diet, and the diets of two other groups were overdosed with Se in the form of sodium selenite (9 mg/kg) and supplemented with Zn (13 mg/kg). Two experimental groups were fed a diet supplemented with Zn (13 mg/kg) and Se at an adequate level (0.009 mg/kg); a half of the animals was supplemented with vitamin E. The results showed significant differences in the Se contents between the rat strains in case of Se-overdosed groups, where in the liver and kidney tissue Se contents of SHR rats exceeded 3- and 7-fold the normotensive ones. The Se uptake was altered by the vitamin E; no effect of Zn was observed. Activities of antioxidant enzymes were determined in the animal tissues indicating different patterns according to rat strain, tissue analysed, and administered Se dose. Thus, Se overdose, for instance, *via* an incorrectly prepared dietary supplement, can result in serious imbalances of the biochemical status of the animals.

Key words: selenium, zinc, vitamin E, Rattus norvegicus, biochemical parameters

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Introduction

Selenium is an essential trace element. The relationship between its intake and influence on humans has become the subject of research since the end of the last century. It has been observed that a low selenium content in the diet of inhabitants of some states is a risk factor in the development of various diseases. However, excessive dietary selenium intake may be toxic in humans and animals. *In vitro*, selenium compounds, such as selenite, selenium dioxide and diselenides, react with thiols (e.g. glutathione) producing superoxide and other reactive oxygen species. The liver, which is the major glutathione producing organ, is also the major target organ of selenium toxicity (Spallholz 1997). The production of reactive oxygen species is connected with the carcinogenicity of excessive Se (Brozmanová 2010). In animals, an excessive intake of Se (or Se toxicity) can lead to the condition of selenosis, which can be divided into two clinical types: chronic, known as the alkali disease; and acute, referred to as blind staggers (Żarczyñska et al. 2013).

Raisbeck (2000) identified accidental or intentional overuse of nutritional supplements as the main sources of selenosis in livestock, whereas the occurrence of cases caused by "natural" sources, such as feedstuff from seleniferous areas, was less common. Although risk of acute selenosis was identified in some seleniferous areas in China (Cui et al. 2017), Longnecker et al. (1991) reported no clinically significant changes in laboratory tests or frequency of symptoms related to enhanced selenium uptake by adults residing in a seleniferous area in the US. In contrast, Aldosary et al. (2012) reported selenosis symptoms in patients consuming a Se-overdosed nutritional supplement, where the cumulative dose of ingested selenium was 1.3 gram per capita over a mean period of 37.5 days. Cases of human patients overdosed by Se *via* the intake of nutritional supplements have also been published by other authors (Veatch et al. 2005, Morris and Crane 2013). Similarly, the occurrence of Se-overdosed feedstuffs/dietary supplements resulting in selenosis in livestock has already been documented (Mihailovic et al., 1992). As reviewed by Żarczyñska et al. (2013), a single selenium dose of 1–6 mg/kg of body weight is lethal for most animal species, and feed with a selenium content higher than 20–30 mg/kg leads to acute selenosis. Kaur et al. (2003) showed that sub-chronic selenosis was caused by oxidative stress in calves exposed orally to a daily sodium selenite dose (0.25 mg/kg for 16 weeks), as evidenced by a 3-fold increase in lipid peroxidation; activities of glutathione-S-transferase, glutathione reductase, superoxide dismutase and catalase were also significantly increased. Furthermore, blood Se levels were positively correlated with erythrocytic glutathione peroxidase (GPx) activity. In rats, LD_{50} for oral administration is 7 mg/kg of body weight for selenite, and 1.6 mg/kg of body weight for selenate (Richardson and Gangolli 1996). The importance of the particular Se compound administered in the diet on the signs of selenosis has also already been claimed (Panter et al. 1996). The ability of vitamin E to alleviate the toxic effects of Se has previously been observed (Hussein et al. 2014), as well as the complementary effects of Se, Zn, and vitamin E in various biochemical processes (Brodowska et al. 2016).

Many regions worldwide, including the Czech Republic, are characterised by low amounts of Se in the soil, resulting in deficient concentrations of Se in feedstuffs (Száková et al. 2015). Žáková et al. (2016) showed low Se contents in the pasture of horses, where only Se supplementation of the diet led to adequate Se status of the animals, and in this case resulted in the effective elimination of the potential Se deficiency. Thus, the risk of Se overdose in animals of the Czech Republic *via* natural sources of this element is negligible. However, the potential risk of accidental Se overdose by dietary supplements for livestock should be taken into account.

The main objectives of the study were: i) to assess and compare the biochemical responses of rat organisms on dietary Se overdose as compared to an adequate Se fortification of the diet; ii) to understand the potential ability of vitamin E and Zn addition to the diet to influence the biochemical parameters of rats exposed to toxic levels of Se to mitigate the harmful effects of Se; and, iii) to assess the potential effect of Se and/or vitamin E, and Zn dietary intake on hypertensive rats as compared to normotensive rats.

Materials and Methods

Male Wistar Kyoto normotensive rats and spontaneously hypertensive rats (SHR) were obtained from a breeder (Velaz, Prague, Czech Republic) at 30 days of age and housed in cages (one animal per cage) in a room with a controlled temperature (varying from 23 to 25°C) under natural light conditions. Forty-eight animals of each strain, divided into six groups (labelled A, B, C, D, E, F), were used. The rats were fed the semi-synthetic diet according to the experimental design for 60 days. Feed and water were supplied to the animals *ad libitum*. Feed consumption and body weight of the animals were monitored weekly. The composition and nutritional values of the diets are summarised in Table 1. The control group was fed the untreated semi-synthetic diet (Group A). Groups B and C were fed a diet overdosed with Se as sodium selenite (9 mg/kg of Se) and supplemented with Zn (13 mg/kg of Zn),

Table 1. The nutritional values of the experimental diets according to the groups of animals.

	Group A	Group B	Group C	Group D	Group E	Group F
Crude protein (g/kg)	19.0	19.0	19.0	19.0	19.0	19.0
Crude fat (g/kg)	33	33	33	33	33	33
Crude fiber (g/kg)	49	49	49	49	49	49
Crude ash (g/kg)	64	64	64	64	64	64
Starch (g/kg)	365	365	365	365	365	365
Sugar (g/kg)	47	47	47	47	47	47
Vitamin A (IU/kg)	25000	25000	25000	25000	25000	25000
Vitamin D_3 (IU/kg)	1500	1500	1500	1500	1500	1500
Vitamin E (mg/kg)	125	125	161	161	161	125
Vitamin K3 (mg/kg)	20	20	20	20	20	20
Zn added (mg/kg)	-	13	13	-	13	13
Se added (mg/kg)	-	9	9	-	0.009	0.009

where group C was additionally supplemented with vitamin E (36 mg/kg). Group D was fed the untreated diet supplemented with vitamin E (36 mg/kg). Groups E and F were fed the diet supplemented with Zn (13 mg/kg of Zn) and Se at an adequate level (0.009 mg/kg of Se), where group E was additionally supplemented with vitamin E (36 mg/kg). After the termination of the experiment, the animals were euthanized by exsanguination after anaesthetizing with Xylapan (xylasin) and Narketan (ketamin), and liver and kidney were sampled. The whole experiment was conducted in accordance with Animal Care and Protection Act, §17 Czech code 246/1992, and 162/1993 (whole code reading No. 167/1993).

The sampled tissues were kept at −18 °C and subsequently freeze-dried and homogenised. To determine the contents of Se and Zn in the freeze-dried and homogenised animal tissues and diets, the individual samples were decomposed in an Ethos 1 (MLS GmbH, Germany) microwave-assisted wet digestion system (Rýdlová et al. 2017). To determine total Se concentrations in the digests, inductively coupled plasma-mass spectrometer (ICP-MS) was applied using an ELAN DRC-e instrument (Perkin Elmer, Concord, Canada). An inductively coupled plasma-atomic emission spectrometer (ICP-OES; Agilent 720, Agilent Technologies Inc., USA) was applied for determination of Zn in the digests. The activities of selected antioxidant enzymes, glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), thioredoxin reductase (TrxR), and catalase (CAT) were measured in extracts of the liver and kidney. The tissue extracts were prepared by homogenisation of 0.08 g of the liver or kidney with 1 mL of buffer (Rýdlová et al. 2017). The specific enzymatic activities in the tissue extracts were determined using spectrophotometers Libra S22 (Biochrom, UK) and PowerWave XS (BioTek, USA). Catalase activity was determined according to Góth (1991) at λ = 240 nm. Glutathione peroxidase activity was determined at λ = 340 nm by the modified method published by Flohé and Günzler (1984). Glutathione reductase activity was determined at λ = 412 nm according to Cribb et al. (1989). Thioredoxin reductase activity was measured at λ = 412 nm according to Luthman and Holmgren (1982). Glutathione S-transferase activity was measured at λ = 340 nm according to Habig et al. (1974). All the analyses were performed at 25°C.

The data were processed using Gen5 Data Analysis (BioTek, USA), Microsoft Office Excel 2007 and Statistica 12 CZ statistical software. One-way analysis of variance (ANOVA) at $p<0.05$ followed by Scheffé's test was applied. The Shapiro-Wilk test ($p<0.05$) was used to verify the normality of the data distribution.

Results

The results showed lower body weights in SHR rats as compared to the normotensive Wistar animals (Fig. 1). For normotensive rats, all the experimental groups tended to have lower body weights as compared to the control group, whereas the Se overdose in groups B and C did not result in a significant decrease in body weight. In contrast, significantly lower ($p<0.05$) body weights in group B were recorded in case of SHR rats, whereas the body weights in group C, with addition of both Zn and vitamin E, tended to increase as compared to group B. In the control diet, the Se and Zn

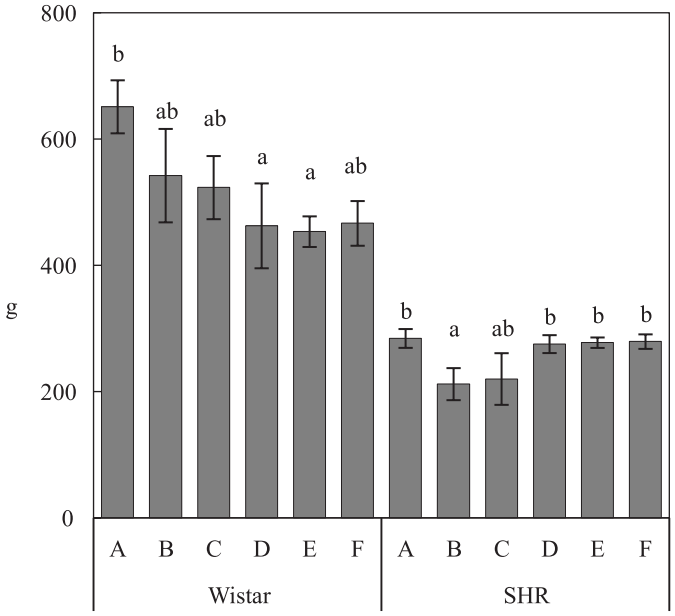

Fig. 1. The average body weights of rats in the end of experiment according to the diets A, B, C, D, E, F. The averages marked by the same letter did not significantly differ at $p<0.05$ within individual rat strains; data are presented as mean ± standard deviation, n=8

Table 2. The element contents in rat liver according to the individual variants (mg/kg of dry matter).

Diet	Wistar		SHR	
	Se mg/kg	Zn mg/kg	Se mg/kg	Zn mg/kg
A	1.75 ± 0.27^{a}	68.1 ± 9.5^{ab}	1.85 ± 0.25^{a}	59.0 ± 11.4^{a}
B	7.87 ± 1.40^{c}	55.1 ± 3.2^{a}	21.4 ± 2.60^{c}	70.7 ± 9.7^{ab}
C	6.45 ± 1.28^{c}	57.6 ± 9.5^{a}	12.0 ± 1.70^{b}	66.4 ± 9.8^{ab}
D	3.09 ± 0.59^{ab}	74.9 ± 6.3^{b}	3.16 ± 0.44^{a}	66.3 ± 5.2^{ab}
E	3.45 ± 0.86^{b}	63.4 ± 4.8^{ab}	2.87 ± 0.31^{a}	69.1 ± 5.3^{ab}
F	3.33 ± 0.76^{b}	67.3 ± 4.4^{ab}	3.97 ± 0.42^{a}	81.1 ± 5.9^{b}

The averages marked by the same letter did not significantly differ at $p<0.05$ within individual columns; data are presented as mean ± standard deviation, n=8

contents were 0.082 ± 0.014, and 60.4 ± 2.43 mg/kg, respectively. Thus, the Zn addition (13 mg/kg of Zn) resulted in a slight increase in the daily intake of this element, whereas the Se-overdosed diets (9 mg/kg of Se) contained levels that were two orders of magnitude higher than the control levels. The differences in the Se and Zn doses administered to the animals resulted in various accumulations of these elements in the rat tissues (Tables 2 and 3). The results showed elevated Se contents ($p<0.05$) in both the liver and kidneys of Wistar rats exposed to both adequate and overdosed Se levels as compared to the control, whereas for the SHR rats, these groups tended to increase without statistical verification of the differences. Moreover, group D administered with an elevated vitamin E dose (without alteration of the Se level) indicated the positive effect of vitamin E for Se utilisation in the rat organism. As expected, the Se overdose (i.e. groups B and C) resulted in significantly increased ($p<0.05$) Se contents in both the liver and kidneys. The results also documented significant differences between the investigated rat strains in case of Se-overdosed groups B and C, where in group B, the liver and kidney Se contents in SHR rats exceeded 3-fold and 7-fold those found in the normotensive animals, respectively. The Se levels in the SHR rats of group C were decreased as compared to group B indicating the potential role of vitamin E in this case. Slight increases (significant in some cases) in liver and kidney Zn contents were recorded in SHR rats in all the groups as compared to the control (Tables 2 and 3). Similar results were determined in the kidneys of the normotensive rats. However, a significant decrease in liver Zn contents was observed in Se-overdosed Wistar rats (groups B and C).

The study revealed a significant increase ($p<0.05$) in the specific GPx activity in the animals with an ade-

Table 3. The element contents in rat kidney according to the individual variants (mg/kg of dry matter).

Diet	Wistar		SHR	
	Se mg/kg	Zn mg/kg	Se mg/kg	Zn mg/kg
A	3.74 ± 0.34^{a}	67.5 ± 8.0^{a}	4.52 ± 0.51^{a}	44.7 ± 8.2^{a}
B	7.63 ± 1.40^{cd}	72.8 ± 3.2^{ab}	51.5 ± 2.0^{b}	39.2 ± 11.6^{a}
C	9.21 ± 1.28^{d}	72.2 ± 9.5^{ab}	37.0 ± 2.0^{b}	47.9 ± 11.0^{a}
D	5.98 ± 0.77^{b}	71.8 ± 9.7^{ab}	5.35 ± 0.98^{a}	81.6 ± 8.9^{b}
E	6.16 ± 0.50^{bc}	77.8 ± 4.3^{ab}	6.20 ± 0.27^{a}	74.1 ± 4.4^{b}
F	6.39 ± 0.74b^{c}	86.1 ± 3.3^{b}	6.12 ± 1.15^{a}	83.8 ± 4.9^{b}

The averages marked by the same letter did not significantly differ at $p<0.05$ within individual columns; data are presented as mean ± standard deviation, n=8

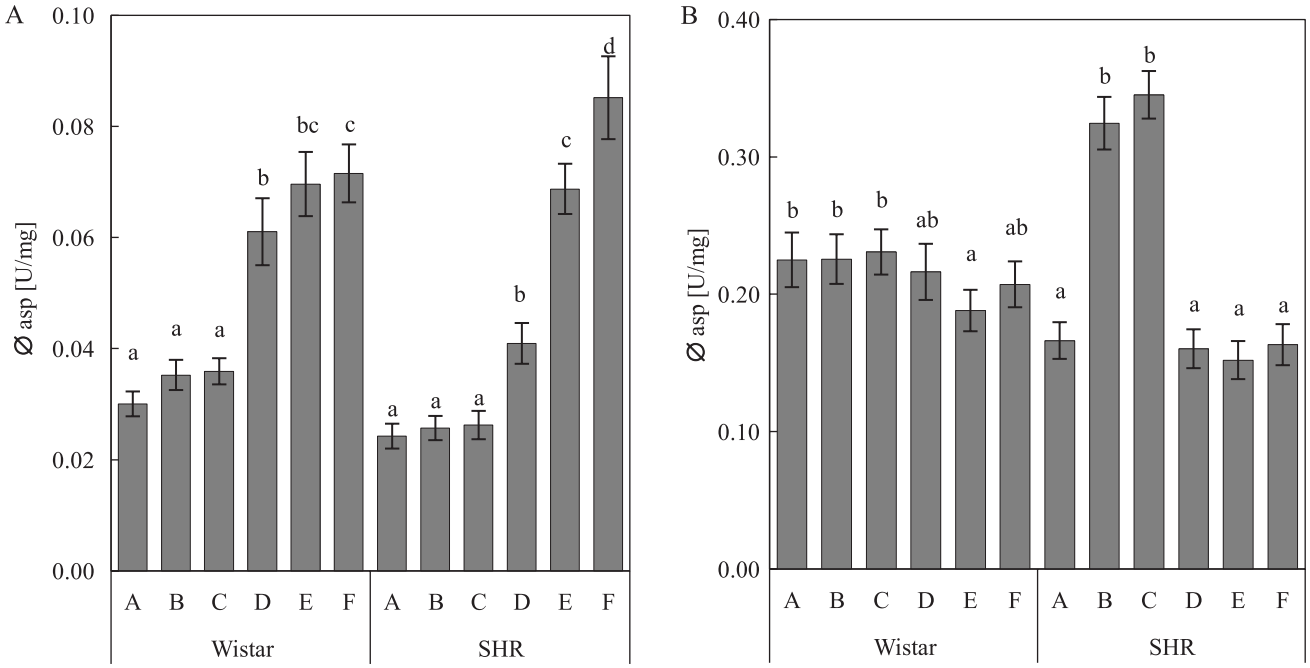

Fig. 2. The specific activity of GPx in liver (A) and kidney (B) of rats (U/mg) according to the diets A, B, C, D, E, F
The averages marked by the same letter did not significantly differ at $p<0.05$ within individual rat strains; data are presented as mean ± standard deviation, n=8

quate Se diet as compared to the control (Fig. 2). The addition of Zn and/or vitamin E resulted in a significant increase ($p<0.05$) in the specific GPx activity in the liver of both strains as compared to the control and Se-overdosed animals. A different pattern of GPx activity was recorded in the kidneys (Fig. 2), where the significant increase ($p<0.05$) in GPx activity as compared to the control was determined in the Se-overdosed groups of SHR rats, whereas no impact of Se overdose on the GPx activity was observed in the normotensive rats (Table 3). Significant increase ($p<0.05$) in TrxR activity (Fig. 3) was determined in the liver of Se-overdosed Wistar rats (groups B and C), and a decrease in the kidneys. No significant differences were found in other groups of Wistar rats. However, the TrxR activity in the SHR rats showed a different pattern, where a significant increase ($p<0.05$) in the liver and decrease in the kidneys were observed in the groups D, E, F, i.e. with adequate Se and/or vitamin E diets. In contrast, the activity of TrxR in the kidneys of the Se-overdosed rats was significantly increased ($p<0.05$) as compared to the control.

The activity of GR (Fig. 4) in the liver and kidneys of the experimental animals differed according to the animal strain and administered Se dose. In the liver of the normotensive rats, the GR activity increased significantly ($p<0.05$) in both Se-overdosed animals (groups B and C), and in those which received an adequate Se dose (groups E and F). There was a similar trend with lower differences among the selenised groups of SHR rats. In the kidneys of both strains, the sole administration of vitamin E resulted in a lower ac-

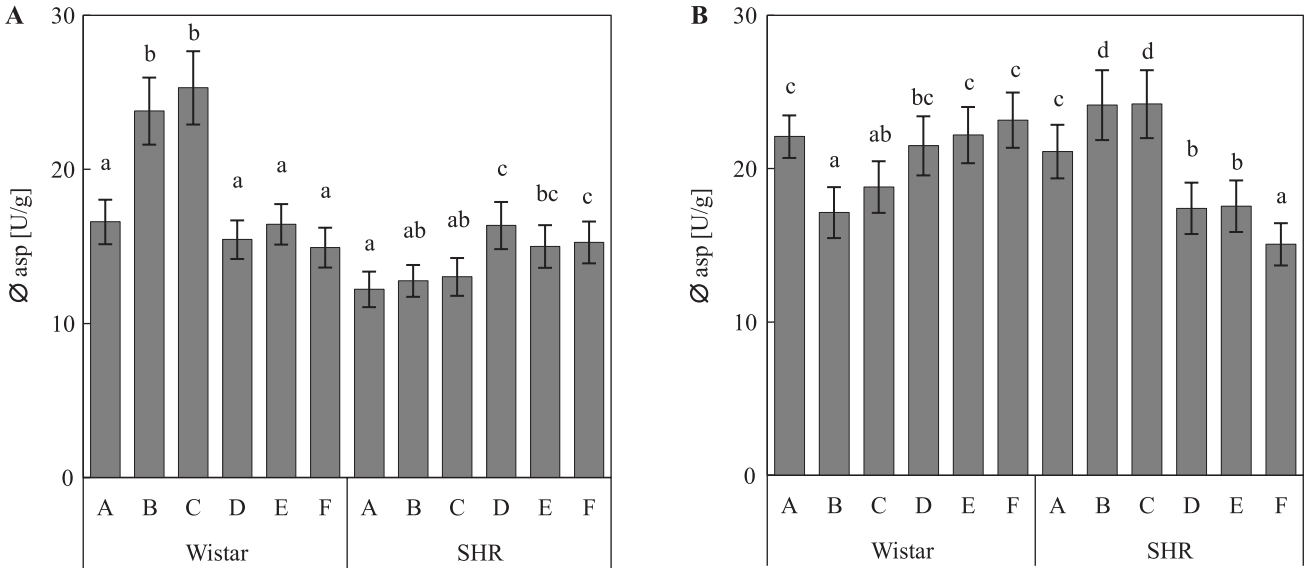

Fig. 3. The specific activity of TrxR in liver (A) and kidney (B) of rats (U/g) according to the diets A, B, C, D, E, F
The averages marked by the same letter did not significantly differ at $p<0.05$ within individual rat strains; data are presented as mean ± standard deviation, n=8

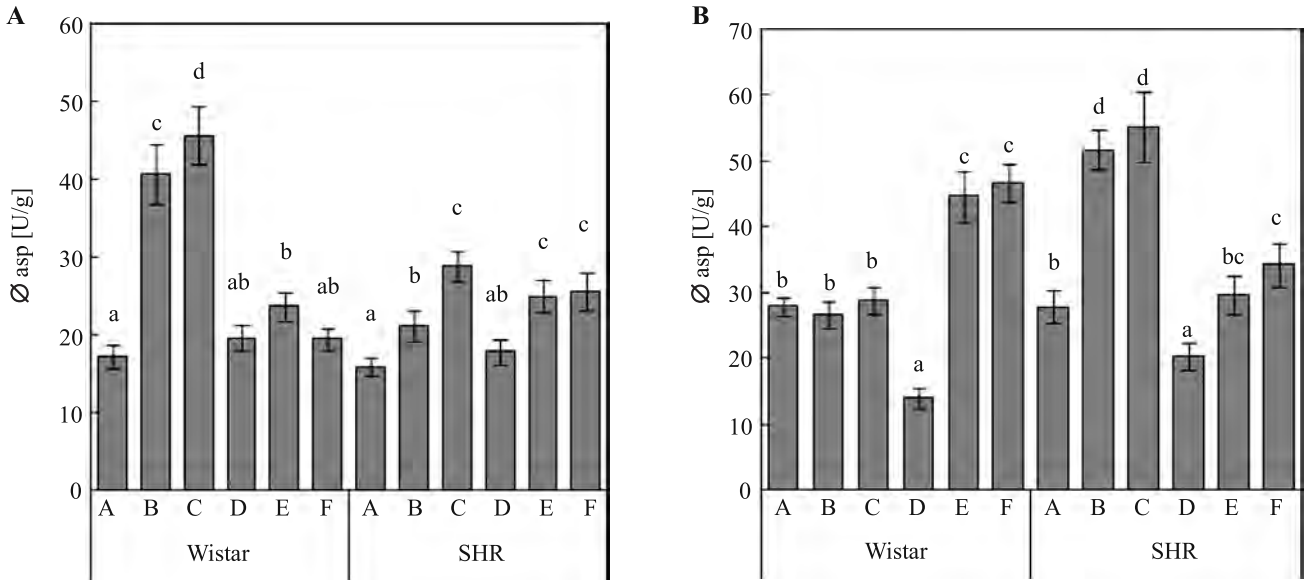

Fig. 4. The specific activity of GR in liver (A) and kidney (B) of rats (U/g) according to the diets A, B, C, D, E, F
The averages marked by the same letter did not significantly differ at $p < 0.05$ within individual rat strains; data are presented as mean ± standard deviation, n=8

tivity of GR. The GR activity in the kidneys of the Wistar rats increased significantly ($p<0.05$) in groups E and F, i.e. administered with an adequate Se dose. In the SHR rats, the GR activity in the kidneys also tended to increase in groups E and F, but less apparently than in the normotensive rats. However, a significant increase ($p<0.05$) in the GR activity was observed in the Se-overdosed groups B and C of the SHR rats.

The increased Se uptake resulted in a significant increase ($p<0.05$) in GST activity in the liver in all the Se administered groups of both strains regardless of the Se dose (Fig. 5). However, in Wistar rats the results showed higher activity in GST in the liver of Se-overdosed rats as compared to that found in the animals administered the lower Se dose, and the opposite pattern was recorded for GST activity in the liver of SHR rats. Moreover, the enhanced vitamin E level in the rat diet led to an increased activity in GST ($p<0.05$) in the liver of SHR rats (group D), whereas no effect of vitamin E administration on the liver GST activity, when as compared to the control, was recorded for the normotensive rats. In the kidneys of the Wistar rats, a significant increase ($p<0.05$) in GST activity was observed in all the Se administered groups of both strains, but in

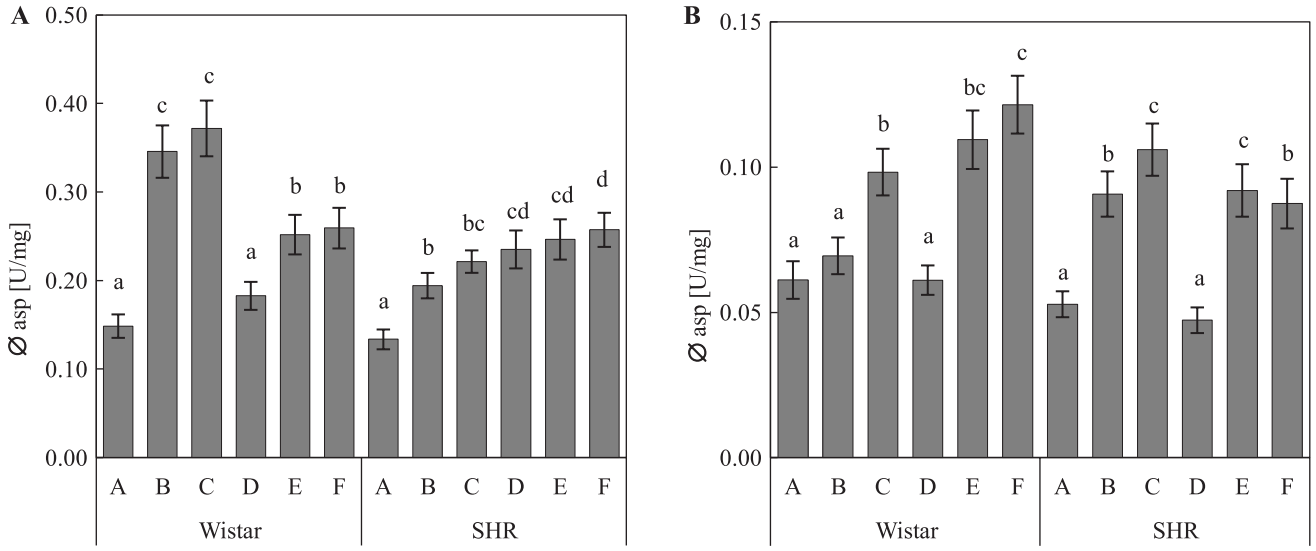

Fig. 5. The specific activity of GST in liver (A) and kidney (B) of rats (U/mg) according to the diets A, B, C, D, E, F
The averages marked by the same letter did not significantly differ at $p < 0.05$ within individual rat strains; data are presented as mean ± standard deviation, n=8

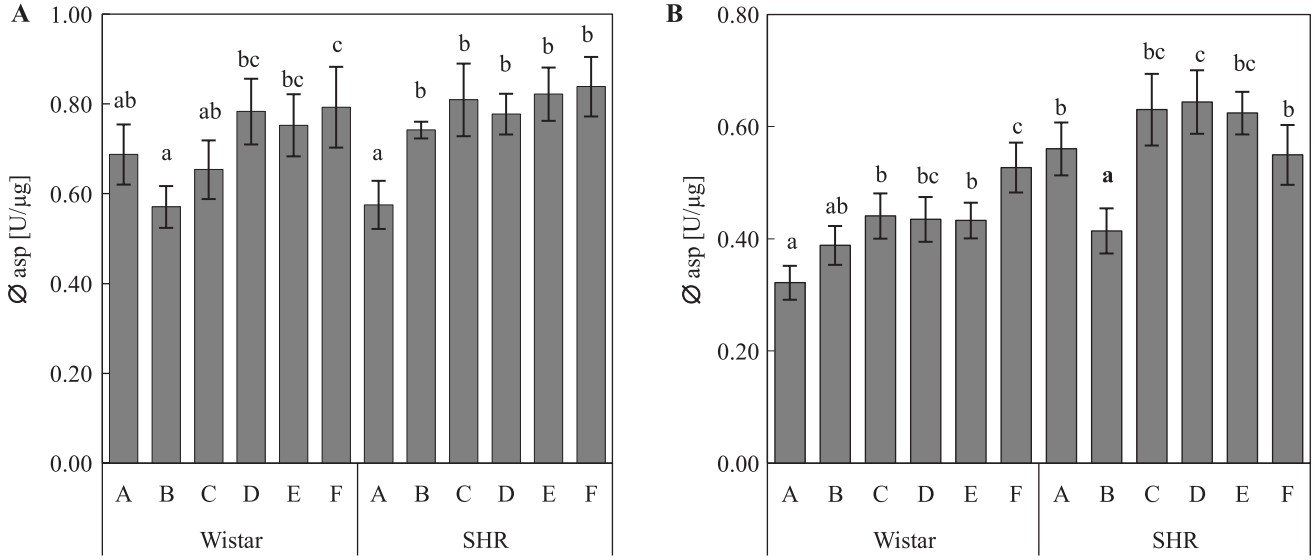

Fig. 6. The specific activity of CAT in liver (A) and kidney (B) of rats (U/μg) according to the diets A, B, C, D, E, F
The averages marked by the same letter did not significantly differ at $p < 0.05$ within individual rat strains; data are presented as mean ± standard deviation, n=8

contrast to the liver, higher levels in the GST activity were determined in the groups with adequately elevated Se uptake (groups E and F), as compared to the Se-overdosed groups B and C. A similar pattern was recorded for SHR rats, where no differences were observed between Se-overdosed and Se-adequately enhanced groups.

With the exception of the liver in the normotensive rats, the CAT activity significantly increased ($p<0.05$) in all the treated groups as compared to the control (Fig. 6). The results indicated lower values in CAT activity in the liver of Se-overdosed Wistar rats, but these differences were not statistically significant. Ambiguous results in CAT activity were determined in the kidneys of the experimental animals, where all the groups of Wistar rats supplemented with Se (regardless of the dose), Zn, and/or vitamin E, i.e. groups B-E, showed elevated CAT activity as compared to the control.

Discussion

Zhang et al. (2013) observed an increase in liver GPx activity in mice exposed to moderate Se doses and decreasing GPx activity in the liver of Se-overdosed mice. Turan et al. (2001) found that a decrease in the liver GPx activity in Se-overdosed rats was not modu-

lated by the addition of vitamin E. According to Skalny et al. (2015), the increased serum GPx activity of Zn-supplemented rats could be connected with the modulation of Se status in the Zn-supplemented animals. Many authors have reported no change in GPx activity in the kidneys of Se-overdosed rats in contrast to the liver, most probably due to differences in the regulation of selenoprotein levels in these two tissues (Štajn et al. 1997, Gan et al. 2002, Venardos et al. 2004). Although these authors administered lower doses of Se to the rats as compared to this study, similar conclusions can be stated in this case with regard to the Wistar rats.

According to Zhang et al. (2008), TrxR takes part in the reduction of the overdosed Se to less toxic compounds. Either no effect or a slight decrease in TrxR activity in the liver and kidneys of Se-overdosed rats have been reported (Gan et al. 2002, Venardos et al. 2004), but the administered Se doses in the cited experiments were lower as compared to those used in this study. However, Berggren et al. (1999) demonstrated an increase in TrxR activity in the liver and kidneys with increasing Se uptake, but although the Se uptake continued, the TrxR activity dropped down again to the level similar to the control in the end of the experiment. Thus, the TrxR activity determined in the end of experiment probably did not clearly reflect the response of the rat organism to the inadequately high Se uptake. The GR activity increased significantly with increasing Se uptake. These results differ from the findings of other authors (Turan et al. 2001, Zhang et al. 2013) who described a decrease in GR activity in the liver and kidneys of rats and mice with increased Se uptake. Increasing GST activities with increasing Se uptake have been observed by many authors (Štajn et al. 1997, Can et al. 2005). In the Se-overdosed liver and kidneys, the groups with elevated Se and vitamin E uptake tended to have higher GSH activity values. Increasing GST activity in rats co-administered with Se and vitamin E has previously been reported, for instance, by ElDemerdash (2004). A decrease in CAT activity in the liver of Se administered mice was published by Zhang et al. (2013). Also, Štajn et al. (1997) reported no effect of Se administration on the CAT activity in rat kidneys.

The potential interactions of Se and vitamin E were discussed predominantly in cases of Se deficiency. For instance, the lack of vitamin E exacerbates symptoms of Se insufficiency (Rao et al. 2001). The increased Se + vitamin E contents in the human diet showed a positive effect on the modulation of the injury of the heart tissue due to preceding Se deficiency (Reeves et al. 1989). However, the ability of vitamin E to reduce the Se-induced changes in cortical tissues in rats administered with sodium selenite (2 mg/kg of body weight) and vitamin E (100 mg/kg of body weight) for 2 or 4 weeks was observed by Hussein et al. (2014).

The complementary effects of Zn and Se in the protection of the animal organism against oxidative stress, induced by various chemicals, is widely known (Ahangar et al. 2017). Moreover, increasing Se levels in tissues of Zn supplemented animals have also been reported (Skalny et al. 2015). In contrast, no synergistic effect of Zn and Se co-administration was observed by Darago et al. (2016), and there was even a decrease in liver Zn in lambs supplemented with Se (Chalabis-Mazurek and Walkuska 2014). It could be speculated that Se-Zn interactions in the rat organism depend on the uptake of the individual elements and/or their mutual ratio, and the Se overdose can result in the imbalance of other nutrients in the rat tissues.

The lower body weights in SHR rats were with agreement with those reported by Furedi et al. (2016) and Sundaram et al. (2013). These authors explained the lower body weight in SHR rats with an adequate dietary supply by the dysregulation in energy homeostasis. Significant differences found among the individual groups of the same strain indicate different responses of the animals to the composition of the diets. Zhang et al. (2008) considered a decrease in the body weight as one of the possible symptoms of Se toxicity.

Regarding the control groups, lower levels in GPx activity were determined in both the liver and kidneys of SHR rats as compared to the Wistar animals, as observed by Lee et al. (2010) and Sundaram et al. (2013). In contrast to the GPx and TrxR activities, no differences in GR activity were reported between control groups of Wistar and SHR rats, as also observed Lee et al. (2010). Similarly as in case of GR, no differences were reported between GST activity in control groups of Wistar and SHR rats (Lee et al. 2010). In the case of CAT activity, the study has revealed higher activity in the kidneys of SHR rats as compared to the Wistar rats. Similar findings were published by Sundaram et al. (2013).

Summarising and concluding the results, significant changes ($p<0.05$) in the selected biochemical parameters of rats differed according to the investigated strain, analysed tissue, and administered Se dose. Apparently, the differences in the biochemical responses between the rat strains can be derived from the different response of these animals to the Se administration, especially in case of SHR rats, confirming differences in the nutritional and biochemical status between the rat strains. The Wistar rats showed a lower ability to accumulate the excessive amounts of Se in the tissues, but the impact on the biochemical parameters was in some cases even higher as that found in the SHR rats. In contrast, the enhanced Zn administration did not

indicate any association with the biochemical response of rats. However, the addition of vitamin E to the rat diet altered the response in GST and GR activities (Figs. 4 and 5) on the excessive dose of Se, as well as the accumulation of Se in the liver and kidneys of the SHR rats. Generally, the results confirmed different biochemical responses in rats to the dietary Se-overdose as compared to those observed for the Se-adequate diet. Moreover, the addition of vitamin E and/or Zn to the diet was able to alter these responses. Significant differences between the biochemical response of Wistar and SHR rats could be related to the different metabolism of both strains (Loyke 1992).

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