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Selenomethionine administration decreases the oxidative stress induced by post mortem ischemia in the heart, liver and kidneys of rats

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Abstract Selenium is an essential element in human and animal metabolism integrated into the catalytic site of glutathione peroxidase (GPX1), an antioxidant enzyme that protects cells from damage caused by reactive oxygen species (ROS). Oxidative stress refers the imbalance between ROS and antioxidant defense systems. It generates alterations of DNA, proteins and lipid peroxidation. The imbalance occurs particularly during ischemia and lack of postmortem perfusion. This mechanism is of relevance in transplant organs, affecting their survival. The aim of this research is to evaluate the effect of seleno-methionine (SeMet) as a protective agent against postmortem ischemia injury in transplant organs. Wistar rats were orally administered with SeMet. After sacrifice, liver, heart and kidney samples were collected at different postmortem intervals (PMIs). SeMet administration produced a significant increase of Se concentration in the liver (65%, $p < 0.001$), heart (40%, $p < 0.01$) and kidneys (45%, $p < 0.05$). Levels of the oxidative stress marker malondialdehyde (MDA) decreased significantly compared to control in the heart (0.21 ± 0.04 vs. 0.12 ± 0.02 mmol g^{-1}) and kidneys (0.41 ± 0.02 vs. 0.24 ± 0.03 mmol g^{-1}) in a PMI of 1–12 h ($p < 0.01$). After SeMet administration for 21 days, a significant increase in GPX1 activity was observed in the liver (80%, $p < 0.001$), kidneys (74%, $p < 0.01$) and heart (35%, $p < 0.05$). SeMet administration to rats significantly decreased the oxidative stress in the heart, liver and kidneys of rats generated by postmortem ischemia.

Keywords Selenomethionine · Malondialdehyde · Oxidative stress · Postmortem interval · Transplant organs

Abbreviations

SeMet	Selenomethionine
GPX1	Glutathione peroxidase 1
SeCys	Selenocysteine
ROS	Reactive oxygen species
MDA	Malondialdehyde
TBA	2-Thiobarbituric acid
LC	Liquid chromatography
ICP	Inductively coupled plasma mass
MS	spectrometry
PMI	Postmortem interval

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Introduction

Selenium is an essential element for humans and animals. It has enzymatic and structural functions as a constituent of selenoproteins (Hatfield et al. 2016; Labunskyy et al. 2014). Approximately 25 selenoproteins such as glutathione peroxidase (GPX1), thioredoxin reductases, iodothyronine deodinases, selenoprotein P and selenoprotein W have been identified in mammals. Selenium in the form of selenocysteine (SeCys) is integrated into the catalytic centers of GPX1, an enzyme with important antioxidant function (López-Bellido and López 2013; Papp et al. 2007). GPX1 is the most abundant selenoprotein in mammals. In combination with catalase and superoxide dismutase, it protects cells and tissues from damage caused by reactive species of oxygen (ROS; Apel and Hirt 2004; Townsend et al. 2003).

Oxidative stress is the imbalance between ROS and the antioxidant defense systems of the body that results in peroxidation of DNA, proteins and lipids. This imbalance occurs particularly in transplant organs during ischemia and the lack of postmortem perfusion, affecting surgery outcomes. It is directly associated with endothelial and parenchymal cell damage, increased vascular permeability, inflammatory response and ROS generation (Shi and Xue 2016). ROS contribute to myocardial death during ischemia–reperfusion (I-R) injury (Yellon and Hausenloy 2007; Yu et al. 2019). They can also lead to chronic dysfunction and allograft rejection (Shi and Xue 2016; Vela et al. 2007).

ROS react with cell membrane lipids, mainly with polyunsaturated fatty acids (PUFAs), which contain methylene groups positioned between *cis* double bonds reactive to oxidizing agents (Marnett 1999). The interaction between ROS and PUFAs generates unstable species that react with other fatty acids leading to a chain reaction of lipid peroxidation whose final products are isosprotan and malondialdehyde (MDA). MDA is one of the non-invasive biological markers of lipid peroxidation (Korchazhkina et al. 2003). The most commonly used method for measuring MDA is based on the reaction with 2-thiobarbituric acid (TBA). The MDA-TBA complex can be separated and isolated by liquid chromatography (LC) and identified by UV–Vis spectrophotometry (Tug et al. 2005).

Due to the large shortage of organs compared to the number of patients on waiting lists, different strategies must be applied to increase the viability and survival of allografts (Miranda et al. 2003; Yu et al. 2019). Many strategies have been developed to reduce the effects of I-R injury. These strategies include preconditioning through antioxidant administration to achieve endogenous protection (Balzan et al. 2014), improving metabolism and cellular responses against an ischemic event (Ferdinandy et al. 2014). Studies have shown that Se supplementation prevents oxidant processes in rat brain tissue and decreases the production of MDA in experimental animals (Musik et al. 2013).

To improve the viability of transplant organs, the effects of selenomethionine (SeMet) during postmortem oxidative stress were evaluated in an experimental model. For this purpose, rats were administered with SeMet for different periods of time. After Se administration, rats were sacrificed and liver, heart and kidney samples were collected at different postmortem intervals (PMIs). Total Se concentrations were determined by inductively coupled plasma mass spectrometry (ICP MS). MDA was extracted and determined in these organs by LC. GPX1 activity was also determined. Finally, MDA concentration and GPX1 activity were related to SeMet administration.

Materials and methods

Reagents

SeMet, TBA 98% and 1,1,3,3-tetraethoxypropane 96% (THP) were obtained from Sigma-Aldrich (St. Louis, United States). The standard MDA solution (10 mM) was prepared by diluting 41.2 µl of THP in 25 mL of H_2O in 0.1 N HCl. THP hydrolysis to MDA was performed by introducing the solution into a 50 °C water bath for 1 h.

1X PBS saline phosphate buffer was prepared by placing 8.06 g of NaCl, 0.22 g of KCl, 1.15 g of Na_2HPO_4 and 0.20 g of KH_2PO_4, in a beaker with 800 mL of Milli-Q water. Finally, pH was adjusted to 7.4 with a 10% (v v^{-1}) solution of H_3PO_4, and the volume was completed to 1000 mL.

A 0.7% (w v^{-1}) solution of TBA was prepared using a magnetic hot plate stirrer by dissolving 0.7 g of TBA in 90 mL of water at 60 °C for 50 min. Then, it

was allowed to cool and diluted to a final volume of 100 mL.

Methanol and ultrapure water were acquired from Fisher Scientific (Fair Lawn, NJ, United States). Digestion reagents such as HNO_3 65% (v v^{-1}), H_2O_2 30% (v v^{-1}), perchloric acid 70% (v v^{-1}) and NaOH were obtained from Sigma-Aldrich (St. Louis, United States).

Experimental design in rodents

Sixty female Wistar rats weighting between 180 and 200 g were obtained from the Central Biotherium of the Universidad Nacional de San Luis. Research activity protocols were evaluated by the Institutional Animal Care and Use Committee (Ord. 006-02, Protocol N ° F-293/18 UNSL). The study lasted 21 days. Rats were randomly placed in metal cages with a sterilized chip changed daily. Rooms were bright, clean and ventilated, with a uniform temperature (24 ± 2 °C) during day and night. Rats were fed with balanced chow based on plant and animal elements, with nutrients and vitamins to ensure normal growth. The chow had a Se concentration of 532 ± 65 μg kg^{-1} (determined by ICP MS). The food intake of each rat was between 15 and 25 g day^{-1} (4 to 6 pellets). Basal intake corresponded to 8 to 13 ug Se day^{-1}. Animals received *ad-libitum* quality food. The water supply was completely renewed daily, eliminating the residual contents of beverage bottles. These bottles were disinfected once a week ensuring water quality.

Rats were administered a dose of 75 ug of SeMet kg^{-1} day^{-1} in 1 mL of distilled water with a probe orally. The SeMet dose was estimated on the basis of previous studies (Kim et al. 2000). Higher Se doses did not represent an additional increase in the activity of antioxidant enzymes, including GPX1 (Sunde and Raines 2011). A control group was established (n = 15) and administered orally with 1 mL of water. The remaining rats (n = 45) were divided into three groups and administered with SeMet for a period of 7, 14 and 21 days respectively. At the end of the administration period, the animals were sacrificed by inhalation of carbon dioxide (chemical method). Death was confirmed by cervical dislocation. The liver, kidneys and heart were then removed at different PMIs (0, 1, 3, 6 and 12 h) from different rats. Organs were freeze dried to stop all oxidative processes and stored at − 20 °C prior to analysis.

Sample treatment for total selenium analysis

For the total Se analysis of rat organs, microwave-assisted acid digestion was performed in a Milestone START *D* model digester (Serisole, Italy), equipped with eight polytetrafluoroethylene reactors. The digestion protocol was performed according to the instructions of the apparatus: 0.6 g of animal tissue were weighed and placed into the digester, after which 5 mL 65% HNO_3 and 2 mL of 30% (v v^{-1}) H_2O_2 were added. To perform the digestion process, a ramp of 10 min was defined until reaching the working temperature of 200 °C, which was maintained for 20 min, with a maximum energy of 1000 watts, achieving complete dissolution. Subsequently, a dilution with Milli-Q water was made, prior to Se analysis by ICP MS. The accuracy of the method was confirmed using the certified reference material BCR-185R Bovine Liver (trace elements) from the Community Bureau of Reference, European Comission, obtained from Merck.

Analysis by ICP MS

An ICP MS (Perkin-Elmer SCIEX, ELAN DRC-e Thornhill, Canada) was used for Se determination. The carrier gas Ar with a purity of 99.996% was supplied by Air Liquide (Río Cuarto, Córdoba, Argentina). Table 1 shows the operating conditions of the ICP MS. The following devices were used for sample introduction: an automatic injector (S10 AS-90 Perkin-Elmer autosampler), an HF-resistant high performance fluoroacetate (PFA) nebulizer model PFA-ST and a quartz cyclonic fogging chamber with a drain line and internal cover, cooled with ESI PC3 system (Omaha—NE, USA).

MDA extraction from biological samples

Sample preparation and MDA extraction were performed according to previous studies (Faizan et al. 2014; Korchazhkina et al. 2003; Mateos et al. 2005), with modifications. To perform the extraction, 0.2 g of tissue from the liver, heart and kidneys was homogenized in 2 mL of 1X PBS, pH 7.4, for 5 min. The suspension was then centrifuged at 10000 rpm for

Table 1 ICP MS experimental conditions

ICP-MS (Perkin-Elmer SCIEX, ELAN DRC-e Thornhill, Canadá)	
Radiofrequency power (w)	1050 W
Plasma Ar flow rate	13 L min^{-1}
Auxiliary Ar flow rate	1.35 L min^{-1}
Nebulizer gas flow rate	0.87 L min^{-1}
Sample flow rate	400 µL min^{-1}
Sampler cone	Ni, i.d 1.1 mm
Skimmer cone	Ni, i.d 0.9 mm
Dwell time	500 ms
Number of replicates	3
Isotope monitored	^{82}Se (with krypton correction)

30 min at 4 °C, and supernatants were collected. Subsequently, 500 µL of the supernatants with 100 µL of NaOH 6 M (mol L^{-1}) were transferred to a 1.5 mL Eppendorf tube and incubated for 30 min at 60 °C. Then, 250 µL of 35% (v v^{-1}) perchloric acid was added to precipitate proteins. The mixture was incubated 30 min in an ice bath and then centrifuged at 6000 rpm for 10 min. Next 300 µL of the supernatant was collected and 300 µL of TBA 0.7% (w v^{-1}) was added. The mixture was allowed to react in a thermostatic bath (95 °C) for 40 min. After incubation, 100 µL of sample was injected into the LC system.

Analysis of MDA-TBA by LC in biological samples

A chromatographer Series 200 Perkin-Elmer (Thornhill, Canada), a column C18 ZORBAX Sb-Aq (4.6 × 150 mm 5-Micro) and a UV–Vis spectrophotometer (Model vis 723G, RAYLEIGH) were used for MDA determination. Chromatographic conditions are shown in Table 2. MDA was detected at 532 nm in a micro-optical glass cuvette, black faces, 10 mm continuous flow, z dimension: 15.00 mL.

Analysis of the antioxidant activity of the GPX1 enzyme in tissue homogenates

The determination of the enzymatic activity of GPX1 was based on the spectrophotometric measurement of the oxidation rate of NADPH using tert-butyl hydroperoxide (TBH) as substrate according to the method described by Flohe and Gunzler (Flohé and Günzler 1984). Sodium azide (40 mM) was added to the reaction mixture to inhibit catalase activity. After reaction with hydroperoxide, GPX1 is recycled by gathering reducing equivalents from glutathione (GSH), resulting in the formation of glutathione disulfide (GSSG). This GSSG is reduced back to 2GSH by glutathione disulfide reductase using NADPH as a source of electrons. The rate of oxidation of NADPH is directly associated with the activity of GPX1. A decrease in absorbance at 340 nm is produced by the consumption of NADPH at 37 °C. The difference in NADPH consumption between the blank and the sample determined the enzymatic activity of GPX1. Enzyme activities were expressed as µmol of oxidized NADPH min^{-1} mg of $protein^{-1}$.

Protein concentration was determined according to the Bradford method (Bradford 1976), using bovine serum albumin as standard. All biochemical enzyme

Table 2 HPLC experimental conditions

Time	Flow	Formic acid 0.1% v v^{-1} (%)	Methanol (%)	Curve
7	1.5 mL min^{-1}	40	60	Constant
3	1.5 mL min^{-1}	5	95	Gradient
5	1.5 mL min^{-1}	5	95	Constant
3	1.5 mL min^{-1}	40	60	Gradient

reactions and protein determinations were performed in a 3000 µL quartz cuvette (GPX1 and protein) in a spectrophotometer.

Determination of hepatic enzyme activities

Glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and gamma-glutamyl transferase (GGT) activities were determined. Analyses were performed on the serum of rat blood obtained by cardiac puncture. Analyses were carried out manually using commercial colorimetric kits from Wiener lab. (Rosario, Argentina). Spectrophotometric readings were taken at a wavelength of 505 nm for GOT and GPT activities and at 405 nm for GGT activity.

Statistical analysis

An ANOVA analysis was performed to define significant differences between experimental groups. Previous analysis data groups were verified by the Grubbs test, the Ryan-Joiner test and the test for equality of variances. Results were analyzed as the mean ± standard error, and the statistical significance of differences between groups was calculated using ANOVA with an error rate of $\alpha = 0.05$ (equivalent to a 95% confidence level) subsequent comparison by Tukey- Fisher. The Minitab 17® program was used for statistical and graphical analyses. Graphics from the statistical analysis can be seen in Supplementary Material.

Results and discussion

Selenium distribution in the liver, heart and kidneys of rats

Selenium supplementation in rodents has been frequently reported in the scientific literature (Kim et al. 2000). SeMet is chosen for supplementation because of its higher bioaccessibility in the gastrointestinal tract (Rider et al. 2010; Smith and Picciano 1987). Table 3 shows the Se concentration reached in the heart, liver and kidneys after supplementation. In a first approach, it was observed that the Se concentration of the administered groups showed significant differences with the control group ($p < 0.05$; Fig. 1 SI; Table 3). SeMet administration increased Se concentration in the analyzed organs. The determined Se concentrations are in good agreement with those reported in the literature (Akahoshi et al. 2019; Sunde and Raines 2011). SeMet administration induced a higher accumulation of Se in the liver and kidneys. These organs are the main sites of synthesis for most selenoproteins, especially cellular SELENOP and GPX1 in the liver and extracellular GPX1 in the kidneys (Suzuki et al. 2010). This observation is in good agreement with the studies reported by Deagen et al. (Deagen et al. 1985). SeMet can be non-specifically incorporated into proteins by randomly replacing (sulphur) methionine. Compared to SeCys administration, it does not substitute cysteine in proteins and can be easily degraded to alanine plus hydrogen selenyde by selenocysteine lyase. After achivieng Se accumulation in the target organs, experiments continued to demonstrate the protective effects of SeMet on the heart, kidneys and liver.

Analysis of the antioxidant effects of SeMet at different postmortem intervals

The time elapsed between ischemia and reperfusion in organs determines the fate of transplant surgeries. During PMIs, transplant organs suffer injuries produced by ROS generation and oxidative stress during the anoxia period. It is known that Se deficiency affects the redox status of living systems (Mickiewicz et al. 2014). Although Se deficiency in vivo can be counteracted by other molecular mechanisms sustaining lifespan (Yim et al. 2019), Se supplementation can decrease postmortem oxidative stress through GPX1 in transplant organs. These effects were evaluated during the anoxia period. MDA, an oxidative stress marker, was analyzed in Se-supplemented rat organs. In addition, GPX1 activity was also determined.

Effects of SeMet administration on MDA concentration

Figure 1 shows MDA concentrations. MDA levels in heart and kidney extracts after supplementation showed a 40–60% decrease compared to the control group ($p < 0.05$; Figs. 2, 4 SI). MDA levels in the kidneys and heart showed significant differences against the control ($p < 0.05$; Figs. 2, 4 SI) after administration for 14 days. These results are

Table 3 Selenium concentration mg kg^{-1} in the different organs

Se concentration (mg kg^{-1})					
	Control Grupo A	7 days Grupo B	14 days Grupo C	21 days Grupo D	$p < 0.05$
Heart	0.23 ± 0.03	0.31 ± 0.01	0.39 ± 0.01	0.46 ± 0.03	$P < 0.05$
Kidneys	2.16 ± 0.09	2.45 ± 0.12	3.03 ± 0.22	3.99 ± 0.10	$P < 0.05$
Liver	1.78 ± 0.09	2.26 ± 0.07	2.85 ± 0.14	3.61 ± 0.13	$P < 0.05$

consistent with the findings reported by Su et al. based on decreased lipid peroxidation in rat tissues by Se (Su et al. 2008). It is also consistent with the findings reported by Sakr et al. based on decreased MDA levels and increased activity of antioxidant enzymes after Se administration (Sakr et al. 2011).

MDA levels at a PMI of 0–3 h did not show significant differences between days 14 and 21 ($p > 0.05$; Figs. 2b, c, 4a, 4b SI). This observation suggests that SeMet administration for 14 days is sufficient to decrease MDA levels. In liver extracts after SeMet administration for 14 days, MDA levels were higher than the control ($p < 0.05$; Fig. 3 SI; Fig. 1) and no significant differences were found between days 14 and 21 ($p > 0.05$; Fig. 3a, b, c, e SI; Fig. 1). These results suggest that after administration for 7 days, toxicity in liver might develop due to Se over-supplementation. The liver is the main organ that synthesizes most selenoproteins and regulates the excretion of Se metabolites (Suzuki et al. 2010). For this reason, it was decided to analyze activities of the hepatic enzymes GOT, GPT and GGT in serum to evaluate the liver status. Activities of GOT, GPT and GGT increased after SeMet administration for 14 days compared to the control (Table 4). These observations confirmed that the liver was harmed after SeMet administration for 14 and 21 days, increasing MDA levels in rats. This fact supports the idea that SeMet administration for 7 days is sufficient to decrease the postmortem production of ROS in the heart, liver and kidneys, preventing liver injuries.

Analysis of the effects of SeMet administration on GPX1 activity

The selenoprotein GPX1 integrates a family of peroxidases that reductively inactivate peroxides using glutathione as a source of reducing equivalents (Handy et al. 2009). The presence of Se in the catalytic centers of the enzyme sustains a high relationship between blood and tissue Se concentration with GPX1 activity (Bellinger et al. 2009). SeCys is the active site component of GPX1 (López-Bellido and López 2013; Papp et al. 2007). However, after SeMet administration to rats for 21 days, a significant increase in GPX1 activity was observed in the liver (80%, $p < 0.001$, Fig. 6 SI), kidneys (74%, $p < 0.01$, Fig. 7 SI) and heart (35%, $p < 0.05$, Fig. 5 SI) compared to the control group (Fig. 2). SeMet can be transformed into SeCys via the trans-selenation pathway (Roman et al. 2014).

In rat cardiac myoblast, an increase of GPX1 activity after SeMet administration was reported (Reyes et al. 2019). Although the total Se concentration in the liver and kidneys was similar (Table 3), GPX1 activity was especially elevated in the liver (Fig. 2). The expression of selenoproteins is regulated independently in each organ and is not only dependant on the Se reserves in the different tissues (Barnes et al. 2009; Schomburg and Schweizer 2009).

After SeMet administration for 7 days, the organs removed at a PMI of 0–3 h showed a higher GPX1 activity compared to the control group ($p < 0.05$; Figs. 5, 6, 7 SI; Fig. 2). However, GPX1 activity decreased in the PMI of 3–12 h ($p > 0.05$; Figs. 5, 6, 7 SI). Since postmortem temperature in rats decreases to equate ambient temperature (25 °C), GPX1 activity is not affected by it (Sandre et al. 2004). GPX1 activity in a PMI of 3–12 h decreases according to the physiological changes that occur in ischemia, such as lack of oxygen and pH variations (Huff-Lonergan and Lonergan 2005).

GPX1 activity levels and MDA levels in the heart, liver and kidneys are related, since lower MDA concentration levels are correlated with higher GPX1 activity. This suggest that there is a response of the antioxidant system against increased oxidative stress, especially in the liver. GPX1 activity is elevated in a PMI of 0–3 h (Fig. 2) and MDA levels continue close to MDA levels immediately after death (Fig. 1).

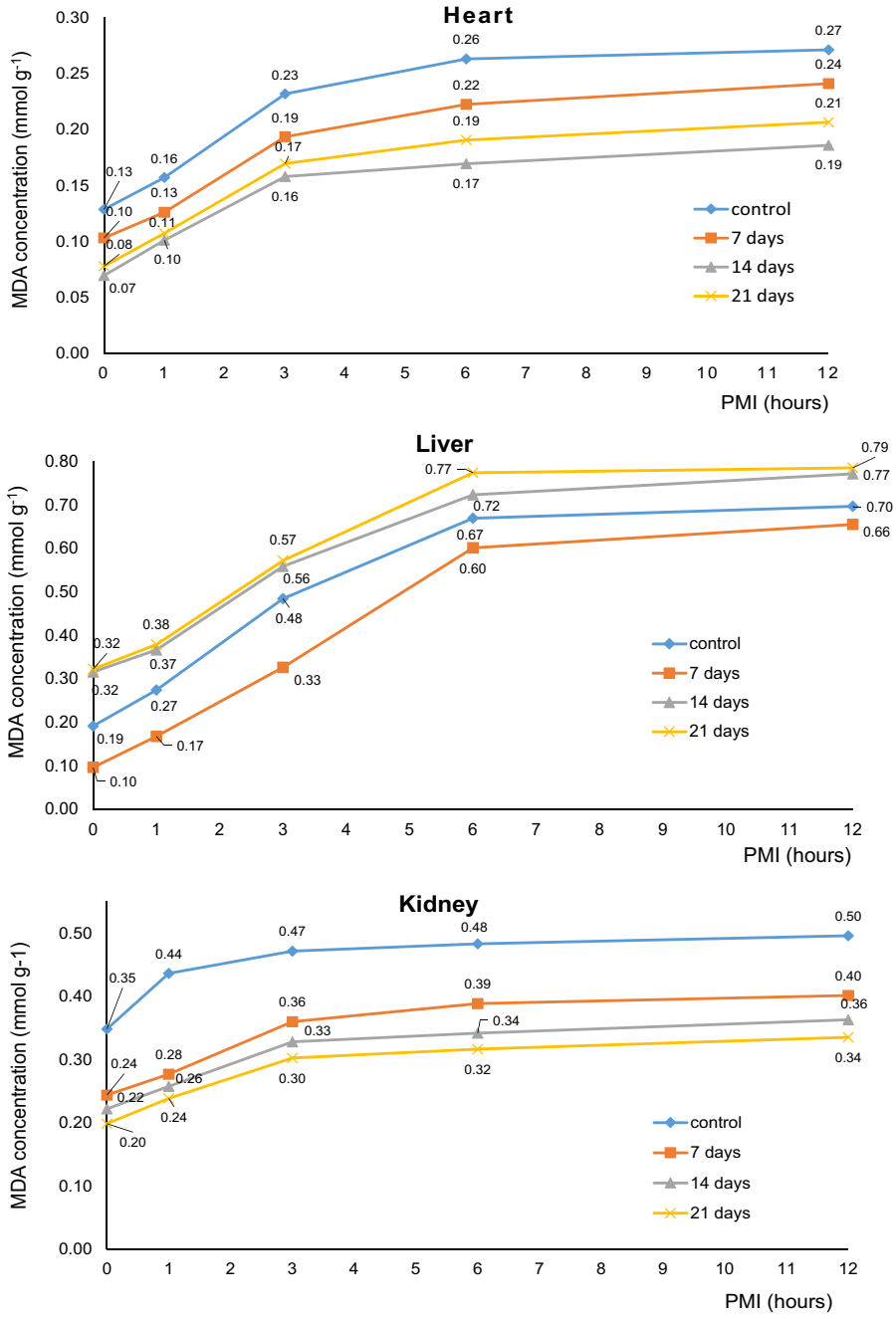

Fig. 1 MDA variations in the heart, liver and kidneys of rats at different PMIs after administration of 75 ug of SeMet kg^{-1} day^{-1} for 7, 14 and 21 days

Considering the time elapsed between donor death and transplant surgery, SeMet administration decrease oxidative stress in the heart, liver and kidneys, improving allograft survival.

Conclusion

In this study, SeMet administration increased Se concentration in the kidneys, heart and liver of rats. This increase was proportional to the number of days SeMet was administered. SeMet administration increased GPX1 activity levels in the heart, liver and

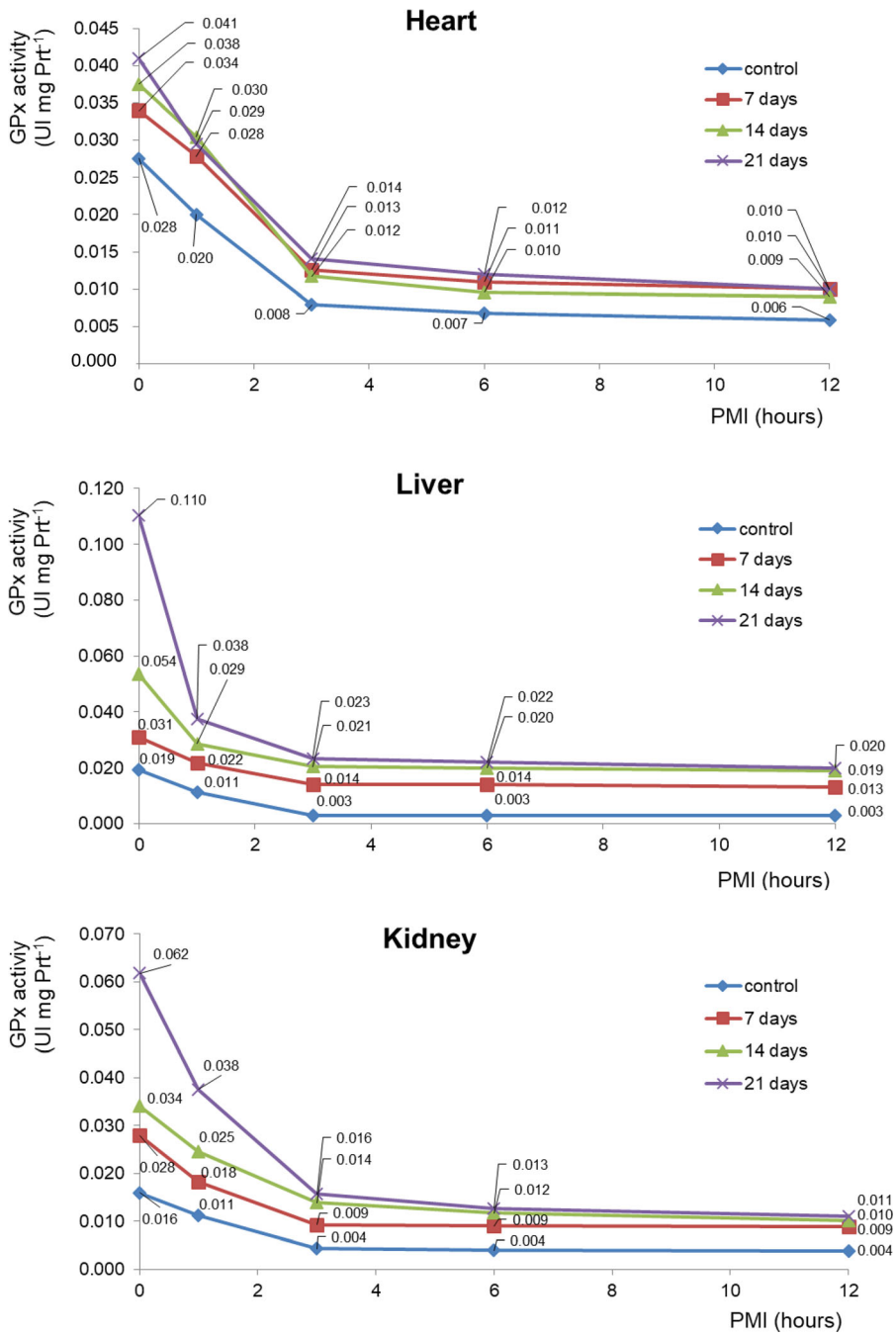

Fig. 2 GPX1 activity variations in the heart, liver and kidneys of rats at different PMIs after administration of 75 ug of SeMet kg^{-1} day^{-1} for 7, 14 and 21 days

kidneys of rats. The highest GPX1 activity levels were reached in the liver.

The concentrations levels of MDA as oxidative stress marker were determined and related to GPX1 activity. MDA levels decrease as GPX1 activity increased. This trend was observed in the PMI of 0–3 h for the heart, kidneys and liver. SeMet administration limited the oxidative stress produced by hypoxia after death. The present study opens a new

Table 4 Hepatic enzyme activities

Activities of the enzymes glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and gamma-glutamyl transferase (GGT)

Days of SeMet administration	Control n = 4	7 days n = 6	14 days n = 6	21 days n = 6
GGT (UI/L)	6.17 ± 1.1	7.21 ± 1.21	*26.4 ± 3.41	*28.2 ± 2.63
GOT (UI/L)	134 ± 12.6	142 ± 7.59	*339 ± 18.7	*354 ± 8.2
GPT (UI/L)	54.9 ± 3.76	61.6 ± 6.58	*114 ± 9.22	*127 ± 8.81

*$p < 0.01$ vs normal control

path to improve the survival of transplant organs and improve the outcome of transplant surgeries.

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Data availability Additional/raw data can be made available upon request.

Declarations

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

Ethical approval All animal experimentation was reviewed and approved by the Animal Care and Use Institutional Committee of the Universidad Nacional de San Luis (Ord. 006-02, Protocol N ° F-293/18 UNSL).

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