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Influence of cadmium, zinc and selenite ions on protein synthesis in mouse liver

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The study aimed at evaluating short-term (24 h) *in vivo* effects of cadmium (Cd^{2+}), zinc (Zn^{2+}), and selenite ions (SeO_3^{2-}) on translational machinery in mouse liver. Activities of translation, $tRNA^{Leu}$ and leucyl-tRNA synthetase (LRSase) were analysed by incorporations of [^{14}C]-labeled leucine ([^{14}C]-Leu) into specific products using liver preparations from mice after intraperitoneal (i.p.) injection of single doses of the following salts solutions: (1) $CdCl_2$ (1.6 mg Cd per 1 kg of body mass); (2) $ZnSO_4$ (3.1 mg Zn per 1 kg of body mass); (3) $ZnSO_4$ and after 20 min $CdCl_2$ (amounts of respective elements indicated above); (4) Na_2SeO_3 (1.25 mg Se per 1 kg of body mass); (5) Na_2SeO_3 and after 20 min $CdCl_2$ (amounts of respective elements indicated before). In respect to control, time-dependent biphasic response of translation in the liver was determined following mice i.p. treatment with $CdCl_2$: diminution by 38% at 2 h followed by a 51% increase at 8 h and by a 32% decrease at 24 h. Neither Zn^{2+} nor SeO_3^{2-} caused remarkable alterations of translation activity when liver had been exposed to those ions for 2 h and 24 h. As compared to the control, Zn^{2+} and SeO_3^{2-} activated translation in mice liver by 67% and by 26% respectively in the 8-h period of exposure. Pre-treatment with Zn^{2+} favoured the resistance of the translation system to Cd^{2+} only at 2 h, while pre-treatment with SeO_3^{2} favoured such a resistance at 2 h and at 24 h of Cd intoxication. The acceptor activity of $tRNA^{Leu}$ decreased by 44–74% and the activity of LRSase by 20–30% within a 24-h period following i.p. injection of $CdCl_2$. An exposure time-dependent decrease of $tRNA^{Leu}$ acceptor activity versus an exposure time-dependent increase of LRSase activity were observed in the preparations from $ZnSO_4$-injected mouse liver. Mice pre-treatment with $ZnSO_4$ prevented activity of LRSase within 24 h against Cd-induced inhibition, but failed in the protection of the acceptor activity of $tRNA^{Leu}$. Responses of those translational components to SeO_3^{2-} were converse and biphasic: the maximum decreasing $tRNA^{Leu}$ acceptor activity (by 66%) a with a simultaneous and insignificant increase of LRSase activity (by 12%), observed after 8 h, were followed by re-activation of tRNA and an insignificant decrease of LRSase activity after 24 h of liver exposure to Na_2SeO_3. In liver preparations from SeO_3^{2-} and Cd^{2+} co-treated mice, Cd inhibitory effects on $tRNA^{Leu}$ were almost abolished within a 24-h period, whilst these effects manifested on LRSase at 2 h and were partly relieved at 8 and 24 h following the treatment.

Key words: cadmium, zinc, selenium, translation, tRNA, leucyl-tRNA synthetase

INTRODUCTION

Cd is a biologically non-essential heavy metal implicated in a number of pathological processes in an organism [1]. In mammals, Cd acts as a nephrotoxic [2], neurotoxic [3] and carcinogenic [4] factor. As cadmium toxicity *in vivo* depends on the duration of exposure [5], the dosage [6], a strain of experimental animals [7], etc., a common model of molecular mechanisms of Cd effect is not yet developed. In such a model, a significant role could be assigned to the system of protein synthesis whose activity integrates changes in the synthesis of stress proteins as well as causative alterations of tissue homeostasis (e. g., necrosis or tumorigenesis). *In vivo* effects of Cd on protein synthesis have been known for many years [8]. However, in protein synthesizing machinery, the molecular targets most sensitive to Cd have not yet been discovered. Previous investigations in our laboratory revealed dose and exposure time-dependent effects of Cd [9]. In the translation phase of protein synthesis, activation of amino acids is considered to be one of control points requiring the

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presence of specific tRNAs and aminoacyl-tRNA synthetases (aaRSases). The latter constitute a family of enzymes actually capable of a broad repertoire of functions: they not only impact protein synthesis, but also extend their effect to a number of non-canonic activities. Specific aaRSs play roles in cellular fidelity, tRNA processing, RNA splicing, RNA trafficking, apoptosis, transcriptional and translational regulation [10]. *In vivo* and *in vitro* studies demonstrated a significant diminution of the activities of both tRNA and aaRSases in response to Cd^{2+} [11, 12]. Contrary to effects on those macromolecules, Cd^{2+} activated particular initiation and elongation factors of translation [13], thereby adjusting the translation process to a new steady-state level. The recently applied reductionistic approach of the *in vivo* examination of the action of toxicants has been disproved by facts about interactions between several toxic ions in an organism. It was shown that pre-treatment with Se and Zn can alter Cd accumulation in tissues, its general toxicology and effects on the antioxidant defense system [14–16]. In regard to Cd altered protein synthesis, co-effects of Se and Zn have not been extensively studied *in vivo*. One of such scarce studies showed that Zn pre-treatment had caused normalization of $tRNA^{Leu}$ and leucyl-tRNA synthetase (LRSase) activities in mice liver under subchronic exposure to Cd [17]. There are, however, no data about effects of Se on those components of the initial stage of translation *in vivo*.

The present study was conducted to investigate acute effects of Cd^{2+}, Zn^{2+} and SeO_3^{2-} on the translation machinery in mouse liver *in vivo*. We demonstrated that both Zn^{2+} and SeO_3^{2-} could counteract the inhibition of translation components caused by Cd. Zn^{2+}, however, exerted a pronounced protection of LRSase, while SeO_3^{2-} could mitigate the inhibitory effects of Cd on $tRNA^{Leu}$ acceptor activity.

MATERIALS AND METHODS

Experiments were done on 4–6-week-old out-bred mice weighing 20–25 g. All experiments were performed according to the Republic of Lithuania Law on the Care, Keeping and Use of Animals (License of State Veterinary Service for working with laboratory animals No 0153).

Mice were randomly assigned into six groups: five experimental and one control. Each group included 6–15 mice. Mice of the first experimental group were injected intraperitoneally (i. p.) with $CdCl_2$ solution (1.6 mg Cd per 1 kg of body mass). Mice of the second experimental group received i.p. injection of $ZnSO_4$ solution at a dose level 3.1 mg Zn per 1 kg of body mass. Mice of the third experimental group received i. p. injection of Na_2SeO_3 solution (1.25 mg Se per 1 kg of body mass). Mice of the fourth experimental group were i.p. injected with $ZnSO_4$ solution and after 20 min with $CdCl_2$ solution in the aforementioned doses. In the fifth group, the same scheme was applied for mice co-treatment with Na_2SeO_3 and $CdCl_2$ solutions containing the indicated amounts of Se and Cd. Control animals (sixth group) received i.p. injection of the same volume of physiological solution.

For the measurement of translation, mice were injected i. p. with [^{14}C]-labelled leucine ([^{14}C]-Leu) (7.4 MBq per kg of body mass) one hour before termination. Translation activity in the mice liver was evaluated by incorporation of [^{14}C]-Leu into newly synthesized peptides and proteins as described in [9]. Leu was selected as an amino acid tag because of its prevalence in cellular proteins of the liver.

The preparation procedures of both total tRNAs and post-mitochondrial supernatant (a source of LRSase) from mice liver were described earlier [18]. Activities of $tRNA^{Leu}$ and LRSase were assessed by aminoacylation reaction using [^{14}C]-Leu [12].

Results were expressed as the mean ± standard error of mean. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

The present study aimed at investigating the *in vivo* effects of Cd^{2+}, Zn^{2+}, and SeO_3^{2-} on translation machinery in the mouse liver. Our experiments revealed a complex response of the translation system to these ions. As Fig. 1 shows, treatment with $CdCl_2$ caused a biphasic response of translation in liver: the decrease to 62% of the control level after 2 h was followed by stimulation of translation up to 151% of the control level after 8 h with subsequent diminution down to 68% of the control level after 24 h of intoxication. In contrast to Cd^{2+}, neither Zn^{2+} nor SeO_3^{2-} caused considerable alteration of translation in the liver after 2 h as well as 24 h of mice intoxication. However, Zn^{2+} and SeO_3^{2-} activated translation by 67% and 26% respectively in the intermediate period (8 h) of liver exposure to these ions. Mice pre-treatment with $ZnSO_4$ prevented Cd-caused inhibition of translation after 2 h and mitigated the effects of Cd in other time-points of exposure. Translation activity in Cd^{2+} and SeO_3^{2-} co-treated mouse liver was almost at the level of SeO_3^{2}-treated group of mice. Thus, both Zn^{2+} and SeO_3^{2-} attenuated effects of Cd on translation after 2, 8 and 24 h of mice administration with $CdCl_2$. In spite of considerable information regarding protective effects of Zn^{2+} and SeO_3^{2-} against Cd cytotoxicity [14, 20] as well as synthesis of proteins [17, 20], the mechanisms of the protection are still unclear. Cd alone can induce oxidative stress when administered to experimental animals in sublethal doses by per-oral and i. p. pathways [21, 22]. Directly Cd does not disturb redox cycling. Therefore, the mechanism of oxidative stress induction by Cd is complicated. Primary effects of Cd can be investigated in acute intoxication *in vivo*. As the affinity of Cd for mercapto groups is several times greater than its affinity for phosphate, chloride, carboxyl, or amino groups [23], Cd binding to mercapto groups on critical biomolecules, particularly those in mitochondria, can cause an oxidative stress, mitochondrial permeability transition, and a decrease in mitochondria respiration [24]. The importance of Cd interaction with mercapto groups in acute hepatotoxicity was

demonstrated by desensitization of mouse liver towards Cd in conditions of metallothionein- and glutathione-overexpression [25, 26]. As Zn^{2+} is a powerful inducer of metallothioneins, we investigated the co-effect of Zn^{2+} and Cd^{2+} on liver protein synthesis (translation) *in vivo*. As already mentioned in this article, Zn^{2+} abolished the Cd-induced depression of translation after 2 h and tended to decrease the Cd-induced activation of translation after 8 h of mice administration with those metal salts, but did not counteract Cd-induced depression of translation 24 h after administration. Considering the fact about the lag-period of metalothionein synthesis induction by metal ions [27], Cd-, Zn- and Cd + Zn-induced activation of translation is probably caused by activation of stress protein synthesis. Zn-induced desensitization of translation to Cd after 2 h of administration can be explained by a decrease in the actual cellular concentration of Cd because of a competition between Zn and Cd for transportation into liver cells [28]. As Zn^{2+} failed to protect translation against Cd^{2+} with exposure time increasing up to 24 h, we assumed that this might be a consequence of accumulation of translation-inhibiting quantities of this metal following induction of metallothioneins.

Altering mercapto-group-rich protein activity, Cd induces oxidative stress by the mitochondrial pathway [26]. Selenoproteins, such as glutathione peroxidase, are important in the antioxidant defense of tissues, thus their activation by injected Na_2SeO_3 can mitigate the oxidative stress-related deleterious effects of Cd. According to our data (Fig. 1), in Na_2SeO_3 pre-treated mice, liver protein synthesis was almost the same as in controls after 2 and 24 h of Cd intoxication. In agreement with considerations about the metal-induced synthesis of metallothioneins, oxidative stress can be assumed as a major mechanism in the initiation of Cd-induced damage to the liver in the acute phase of exposure. High expression of stress proteins may mask the protective effects of Se at the 8th h of liver exposure to Cd, therefore, in our experiments, translation activity in both Cd^{2+}- and Cd^{2+} + SeO_3^{2-}-injected mice was at almost the same levels.

In order to examine the sensitivity of translation machinery components to Cd in Zn^{2+} and SeO_3^{2-} pretreated mouse liver, we determined acceptor activity of $tRNA^{Leu}$ in the aforementioned conditions. The results of examination are shown in Fig. 2. In all time-points of Cd-intoxication, the acceptor activity of $tRNA^{Leu}$ was considerably lower than in controls, with the most pronounced depression at the 8th h (by 74%). Notably, in liver preparations of mice treated with $ZnSO_4$ alone, the acceptor activity of $tRNA^{Leu}$ had been progressively decreasing with increasing the Zn-exposure time. Therefore, it is no wonder that $ZnSO_4$ pre-treatment had a poor effect on Cd-depressed acceptor activity of $tRNA^{Leu}$. In the liver of mice injected Na_2SeO_3 alone, the acceptor activity of $tRNA^{Leu}$ was significantly depressed at only one time-point following Na_2SeO_3 treatment – at the 8th h. Na_2SeO_3 pre-treatment-induced protection of the acceptor activity of $tRNA^{Leu}$ was evident under other time-points of liver exposure to Cd. These effects are unexplainable only in terms of Se-activated antioxidant protection of macromolecules, since at the 8th h of Na_2SeO_3 treatment we detected a diminution of the acceptor activity of $tRNA^{Leu}$. Se is known to prevent Cd accumulation in organs [29]. Whether this mechanism contributes to the diminution of the deleterious effects of Cd on translation we verified by examining $ZnSO_4$ and Na_2SeO_3 pre-treatment

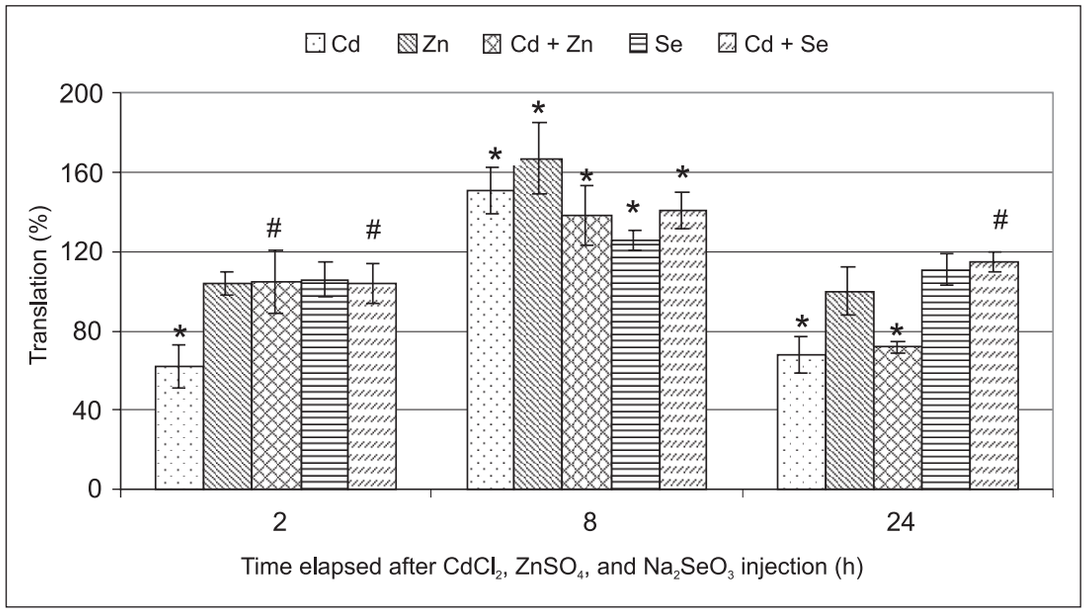

Fig. 1. Dependence of translation rate in mouse liver on the time of exposure to Cd^{2+}, Zn^{2+} or SeO_3^{2-}. The rate of translation in the liver of control mice was set at 100%. Data present results of 6–10 separate experiments; * = differences are statistically significant in comparison with the control mice; # = differences are statistically significant in comparison with the group of Cd-treated mice

effects on LRSase activity. According to data presented in Fig. 3, Zn but not Se efficiently restored Cd-depressed activity of LRSase in all the time points considered. Furthermore, Na_2SeO_3 pretreatment revealed a tendency to strengthen the inhibitory effect of Cd on LRSase after 2 h of intoxication. Howard [30] has reported that *in vivo* glutathione reductase dynamically metabolizes Na_2SeO_3 producing a highly reactive hydrogen selenide (H_2Se) important for the synthesis of selenoproteins. This effect was hardly probable in our experiments as Na_2SeO_3 increased Cd-depressed activities of translation and $tRNA^{Leu}$ as well as activity of LRSase in later time-points of exposure. However, production of reactive H_2Se in an organism can bring about a diminution of LRSase by 20% and 23% in preparations of the liver from mice liver following 2 h of exposure to Se and to Se + Cd, respectively.

We verified *in vitro* whether the effects of $ZnSO_4$ and Na_2SeO_3 pre-treatment on translation components could be direct. The results presented in Table show that Cd decreased activities of both $tRNA^{Leu}$ and LRSase in a concentration-dependent manner. Supplements of $ZnSO_4$ tended to increase

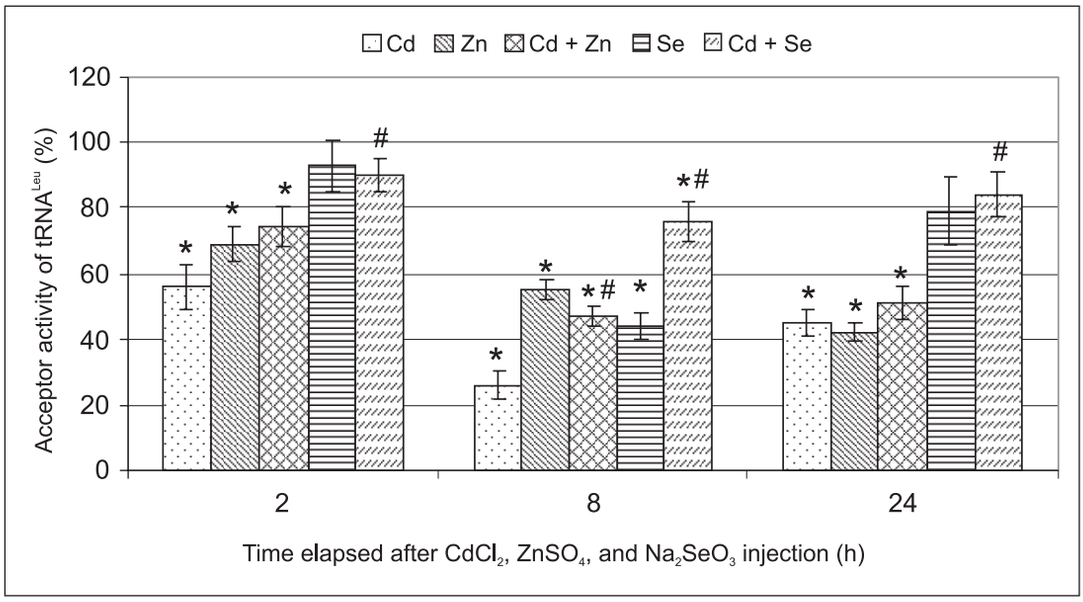

Fig. 2. Dependence of acceptor activity of mouse liver $tRNA^{Leu}$ on the time of exposure to Cd^{2+}, Zn^{2+} or SeO_3^{2-}. Acceptor activity of $tRNA^{Leu}$ isolated from liver of control mice was set at 100%. Data present results of 6–14 separate experiments. Statistics as in Fig. 1

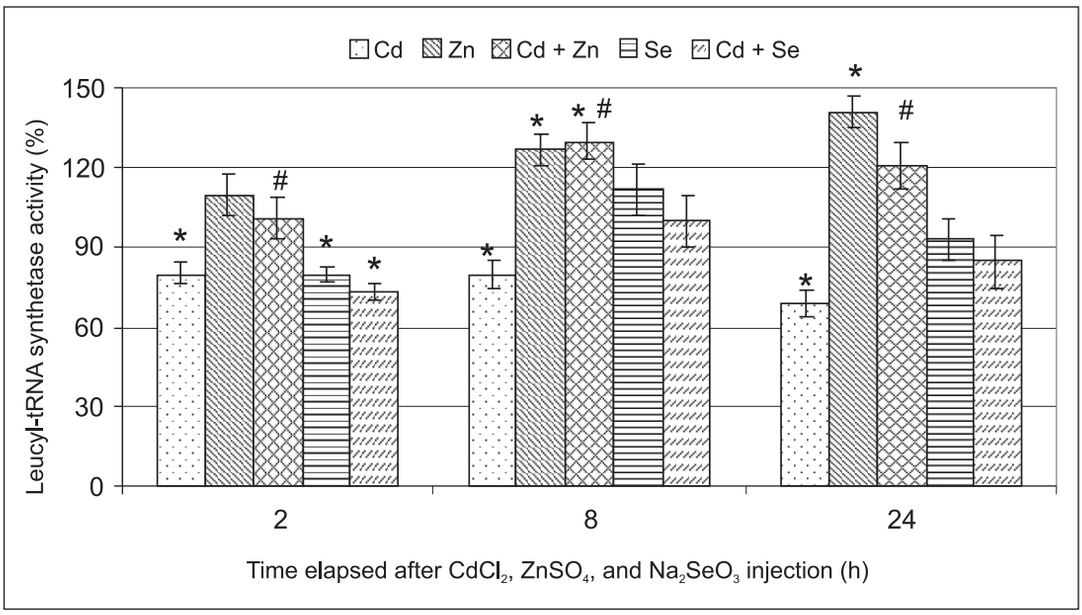

Fig. 3. Dependence of LRSase activity of mouse liver on the time of exposure to Cd^{2+}, Zn^{2+} or SeO_3^{2-}. LRSase activity of liver of control group mice was set at 100%. Data present results of 6–15 separate experiments. Statistics as in Fig. 1

Table. **Effects of Cd^{2+}, Zn^{2+} and SeO_3^{2-} on the activity of $tRNA^{Leu}$ and LRSase isolated from mouse liver. Acceptor activity of $tRNA^{Leu}$ and LRSase activity of liver of control group mice were set at 100%. Asterisks indicate statistically significant differences of values between experimental and control groups. The data present results of 6–8 separate experiments**

Concentration of ions	Acceptor activity of $tRNA^{Leu}$ (%)	LRSase activity (%)
5 μM Cd^{2+}	86 ± 4*	93 ± 3
5 μM Cd^{2+} + 5 μM Zn^{2+}	96 ± 1	101 ± 4
5 μM Cd^{2+} + 2.5 μM SeO_3^{2-}	76 ± 4*	73 ± 9*
10 μM Cd^{2+}	60 ± 6*	61 ± 5*
10 μM Cd^{2+} + 10 μM Zn^{2+}	66 ± 5*	70 ± 7*
10 μM Cd^{2+} + 5 μM SeO_3^{2-}	32 ± 3*	57 ± 4*
20 μM Cd^{2+}	2 ± 0.6*	30 ± 7*
20 μM Cd^{2+} + 20 μM Zn^{2+}	0	18 ± 1*
20 μM Cd^{2+} + 10 μM SeO_3^{2-}	0	36 ± 4*

Cd-depressed activities of both $tRNA^{Leu}$ and LRSase. In a Se-supplemented medium, the inhibitory effects of Cd were increased with preference to $tRNA^{Leu}$ acceptor activity. These results are consistent with the well-known dose-dependent toxic effects of Na_2SeO_3: it causes DNA single strand break [31] and binds to mercapto groups in proteins making an additional place for metal ion attachment [32]. Therefore, *in vivo* effects of both Na_2SeO_3 alone or in combination with $CdCl_2$ are rather a consequence of selenium metabolism than its direct interaction with macromolecules.

CONCLUSIONS

1. Pre-treatment of mice with $ZnSO_4$ solution 20 min before $CdCl_2$ injection prevented activity of translation within 2 h and activity of LRSase within 24 h against Cd-induced inhibition, but failed to protect acceptor activity of $tRNA^{Leu}$.

2. The protective effect of Na_2SeO_3 pre-treatment against Cd-induced inhibition of mouse liver translation components was prevalent for $tRNA^{Leu}$ within 24 h, but insignificant for LRSase.

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KADMIO, CINKO IR SELENITO JONŲ POVEIKIS BALTYMŲ SINTEZEI PELĖS KEPENYSE

Santrauka

Kadmio (Cd^{2+}), cinko (Zn^{2+}) ir selenito (SeO_3^{2-}) jonų poveikis pelių kepenų transliacijos sistemai buvo tiriamas *in vivo* sąlygomis. Transliacijos ir jos sandų $tRNR^{Leu}$ bei leucil-tRNR sintetazės (LRSazės) aktyvumas buvo įvertinamas pagal žymėto leucino [^{14}C-Leu] atsiradimą baltymuose ir peptiduose, susintetintuose kepenyse arba jų preparatuose, išskirtuose iš pelių, kurioms į pilvo ertmę buvo švirkščiami šių druskų tirpalai: 1) $CdCl_2$ (1,6 mg Cd / 1 kg kūno masės); 2) $ZnSO_4$ (3,1 mg Zn / 1 kg kūno masės); 3) $ZnSO_4$ ir po 20 min. $CdCl_2$ (atitinkamų elementų kiekiai nurodyti anksčiau); 4) Na_2SeO_3 (1,25 mg Se / 1 kg kūno masės); 5) Na_2SeO_3 ir po 20 min. $CdCl_2$ (atitinkamų elementų kiekiai nurodyti anksčiau); 6) 0,9% NaCl tirpalas (kontrolė). Veikiant Cd^{2+} *in vivo* sąlygomis, pelių kepenų transliacijos aktyvumas kito taip: praėjus 2 val. sumažėjo 38% lyginant su kontroliniu lygiu (100%), po 8 val. padidėjo 51%, o praėjus 24 val. vėl sumažėjo 32%. Praėjus 2 ir 24 val. po Zn^{2+} arba SeO_3^{2-} sušvirkštimo, pelių kepenų transliacijos aktyvumas liko panašus į kontrolinį lygį, tačiau praėjus 8 val. transliacija buvo atitinkamai 67% ir 26% aktyvesnė. *In vivo* sąlygomis Cd^{2+} veikiant kartu Zn^{2+}, Zn^{2+} tik 2 val. apsaugojo transliaciją nuo Cd^{2+} poveikio. Apsauginis SeO_3^{2-} poveikis buvo reikšmingesnis – šie jonai transliaciją pelės kepenyse apsaugojo praėjus 2 ir 24 val. po $CdCl_2$ sušvirkštimo. *In vivo* sąlygomis per parą Cd^{2+} slopino ir transliacijos sandų $tRNR^{Leu}$ ir LRSazės aktyvumą atitinkamai 44–74% ir 20–30%. Zn^{2+}, priešingai – paveikė šių sandų aktyvumą: slopino kepenų $tRNR^{Leu}$ akcepcinį aktyvumą, bet aktyvino LRSazę. Zn^{2+} tirpalas, sušvirkštas 20 min. iki Cd^{2+} injekcijos, apsaugojo tik LRSazę nuo slopinančiojo Cd^{2+} poveikio. *In vivo* sąlygomis SeO_3^{2-} priešingai veikė $tRNR^{Leu}$ ir LRSazės aktyvumą: po jų 8 val. poveikio $tRNR^{Leu}$ akceptinis aktyvumas sumažėjo 66%, tačiau tuo pat metu LRSazės aktyvumas padidėjo 12%, po 24 val. SeO_3^{2-} $tRNR^{Leu}$ reaktyvino, bet truputį slopino LRSazę. *In vivo* sąlygomis Cd^{2+} kartu su SeO_3^{2-}, SeO_3^{2-} reikšmingai apsaugojo $tRNR^{Leu}$ nuo slopinimo Cd, bet tik iš dalies apsaugojo LRSazę.

Raktažodžiai: kadmis, cinkas, selenas, transliacija, tRNR, leucil-tRNR sintetazė