Influence of cadmium loading on glutathione system of antioxidant protection of the bullocks’ bodies

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It was presented the results of studies of the cadmium effect loading on the activity of the glutathione system of antioxidant protection in young cattle, namely on the activity of glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, the level of reduced glutathione. It was established that feeding of cadmium chloride to bullocks at a dose of 0.03 and 0.05 mg/kg body weight contributed to a decrease in both the enzyme and non-enzyme link of the glutathione antioxidant defense system. The toxic effect of cadmium contributes to a change in stationary concentrations of radical metabolites. 

O2–, ‘OH, HO∙, which, in turn, initiate lipid peroxidation processes. The lowest level of glutathione indexes of the antioxidant defense system in the blood of young cattle was established on the sixteenth and twenty-fourth day of the experiment, it was associated with enhanced activation of liperoxidation and an imbalance between the activity of the antioxidant system and the intensity of lipid peroxidation. The feeding of cadmium chloride to bullocks at a dose of 0.03 and 0.05 mg/kg of animal weight did not affect the activity of the glutathione antioxidant defense system in their blood. It was established that the greater the amount of cadmium chloride in the feed, the lower the activity of the glutathione system of the antioxidant defense of the body of bulls. Thus, cadmium chloride suppresses the antioxidant protection system, in particular, by reducing the activity of the enzyme link: glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, and non-enzyme link: reduced glutathione.

**Key words**: cadmium; superoxidedismutase, catalase, glutathione peroxidase; reduced glutathione, vitamins, selenium.

Introduction

Pollution of agricultural land with heavy metals is mainly due to atmospheric emissions from enterprises (Kabata-Pendias, 2004; Massadeh and Al-Safi, 2005), waste of livestock farms and as a result of the use of mineral fertilizers and toxic chemicals (Hansen et al., 2001; Song et al., 2004). Organic fertilizers – manure and compost, also contain significant amounts of heavy metals. As a result of the introduction of organic matter into the soil, the concentration of such chemical elements as cadmium, lead, copper, zinc, iron, manganese grows in it (Chaney et al., 2001). Considering the slow elimination of heavy metals from the soil, with a long-term supply of even relatively small amounts of cadmium and lead, their concentration over time can reach very high levels.

Environmental pollution by cadmium and its negative effect on the organism of animals, especially young cattle, is an acute problem of studying the pathogenesis of cadmium toxicosis in farm animals as well (Gutij, 2013; Hutyi, 2013). It is known that receipts Cd2+ is associated with the environmental risk to the body through its cumulative toxicity with respect to organs and systems, leads to a decrease in the growth rate and productivity of animals. The accumulation of the above-mentioned heavy metal in the components of the natural environment increases the risk of it entering the body and poses a threat to human and animal health. It negatively affects the efficiency of the livestock industry. Actually, therefore, it is necessary to carry out an in-depth study of the pharmaco-toxicological and biochemical processes that underlie metabolic disor-
The results of many experimental studies indicate that in mammals, cadmium exerts a toxic effect on a number of organs and systems, including the cardiovascular, sexual, excretory, respiratory, hemopoietic, musculoskeletal systems (Fregoneze et al., 1997; Rodriguez et al., 2001; Kumar and Prasad, 2004; Uetani et al., 2005). Hazardous effects include the carcinogenic and mutagenic effects of this element (Peng et al., 2015). However, many aspects of this problem have not yet been clarified.

In the literature there is a large amount of information on the effects of acute and chronic forms of cadmium toxicity of the human body and experimental animals (Ali et al., 1986; Salvatori et al., 2004; Liu et al., 2008). The results of many studies indicate that significant differences in the effects of the metabolism of single-dose high doses and prolonged exposure to low doses of cadmium. It is known that under conditions of intoxication of animals with cadmium compounds, anemia, suppression of the functional state of the immune system and other disorders in the blood formation process occur (Honskyy et al., 2001).

The acute form of cadmium toxicity is sometimes fatal today, however, the syndrome of the chronic form of toxicity occurs much more often (Honskyy et al., 2001; Al-Attar, 2011). Clinical signs of chronic poisoning of animals are accompanied by a sharp decrease in feed intake, weight loss, slower animal growth, impaired kidney function, proteinuria, liver dysfunction, anemia, testicular necrosis, and an increase in neonatal mortality.

The mechanisms of cadmium influence on the antioxidant defense system have recently been intensively studied with laboratory animals (Hutiy, 2012), however, the processes underlying the development of cadmium toxicity in young cattle have not yet been fully clarified. The literature data on the relationship between cadmium-induced damage to liver cells and the activity of the POL processes is often contradictory. Species differences in the response of the antioxidant defense system to the action of the metal, the peculiarities of the metabolic response of the enzyme and non-enzyme of its links to long-term intake have not been studied. Cd2+ in low and high concentrations, determines the relevance of such studies. The study of these processes will allow to uncover deeply unknown features of metabolic processes in cattle under conditions of cadmium loading.

The purpose of the research is to find out the effect of cadmium loading on the activity of the glutathione system of the antioxidant protection of the organism of young animals of cattle.

### Material and methods

Studies were conducted on the basis of a farm Ivanivtsi village, Zhydachivskyi district, Lviv region, with 15 bulls of six months of age, Ukrainian black-speckled dairy breed, which were formed into 2 groups, 5 animals in each:

- **Group 1 – control (K)**, bulls were on a standard diet;
- **Group 2 – research 1 (D1)**, bulls were fed with cadmium chloride feed at a dose of 0.03 mg/kg of animal body weight;
- **Group 2 – research 2 (D2)**, bulls were fed with cadmium chloride feed in a dose of 0.05 mg/kg of animal body weight.

For carrying out research, we adhered to the rules that are mandatory for carrying out zootechnical experiments on the selection and maintenance of animal analogues in groups, the technology of harvesting, use and accounting of feed consumed. The diet of animals was balanced by nutrients and minerals, which ensured their need for basic nutrients.

The experience lasted for 30 days. Blood for analysis was taken from the jugular vein on the 1st, 8th, 16th, 24th, and 30th days of the experiment.

Glutathione peroxidase activity (GP) was determined by the oxidation rate of glutathione in the presence of tertiary butyl hydroperoxide and the content of reduced glutathione in the blood (Vlizlo et al., 2012).

The determination of catalysis activity was performed according to the method (Koroljuk et al., 1988). The principle of the method is based on the ability of hydrogen peroxide to form a stable colored complex with molybdate salts.

The determination of superoxide dismutase activity (SOD) was performed according to the method (Dubinina et al., 1983). The method of determination consists in the restoration of nitrosine tetrizolium by superoxide radicals, which are formed in the reaction between phenazine methisulfate and the reduced form of nicotinamidadiene nucleotide.

The method for determining the content of selenium (Se) consists in the acid mineralization of samples with a mixture of nitric and perchloric acids, the reduction of hexavalent selenium to Se IV and the formation of a complex of selenious acid with 2,3-diaminophthaline-pyrazoselenol, the fluorescence of which is proportional to the selenium content in the sample (Vlizlo et al., 2012). The concentration of vitamins A and E was determined by high performance liquid chromatography (Vlizlo et al., 2012).

All animal manipulations were carried out in accordance with the European Convention for the Protection of Vertebrate Animals used for experimental and scientific purposes (Strasburg, 1986 p.).

Mathematical processing of research results was processed statistically using the Statistica 6.0 software package. The results of the mean values were considered statistically significant at * – P < 0.05,** – P < 0.001 (ANOVA).

### Results and discussion

As a result of our studies, we found that in the feeding of cadmium chloride, the activity of glutathione reductase and glutathione peroxidase was within physiological limits. After feeding cadmium chloride in doses of 0.03 and 0.05 mg/kg of the body weight of the animal, glutathione peroxidase activity on the first day of the experiment increased by 5 and 5.5%, respectively (Table 1). Subsequently, the enzyme activity was studied, gradually
decreased during the whole experiment and on the eighth day of the experiment, respectively, in the research group D1 32.4 ± 1.12 nmol NADPH/min per 1 mg of protein and in the research group D2 31.1 ± 1, 13 nmol NADPH/min per 1 mg of protein.

The lowest activity of glutathione peroxidase in the serum of experimental animals was on the sixteenth and the twenty-fourth days of experience. In particular, in the research group of animals fed cadmium chloride at a dose of 0.03 mg/kg of body weight, the enzyme activity decreased in the indicated periods by 11 and 16%, respectively, in the research group of animals fed cadmium chloride at a dose of 0.05 mg/kg animals enzyme activity decreased by 14 and 20%, respectively.

On the thirtieth day of the experiment, we note a slightly increased activity of glutathione peroxidase, however, compared with the control group, it remained at a low level.

The activity of glutathione reductase in the serum of animals under conditions of cadmium loading, it is shown in Table 2.

Table 1
The activity of glutathione peroxidase in the serum of bulls by cadmium load; nmol NADPH/min per 1 mg of protein (M ± m, n = 5)

| The time of the blood test (days) | Control | Animal Groups |
|----------------------------------|---------|---------------|
|                                  |         | Experimental 1 | Experimental 2 |
| At the beginning of the experience | 36.2 ± 1.20 | 36.4 ± 1.21 | 36.2 ± 1.23 |
| First day                        | 36.1 ± 1.18 | 37.9 ± 1.25 | 38.1 ± 1.21 |
| eighth day                       | 36.3 ± 1.19 | 32.4 ± 1.12** | 31.1 ± 1.13** |
| the sixteenth day                | 36.4 ± 1.21 | 30.5 ± 1.14** | 29.2 ± 1.15* |
| Twenty fourth day                | 36.2 ± 1.22 | 28.7 ± 1.20** | 27.9 ± 1.24** |
| thirty day                       | 36.5 ± 1.25 | 32.1 ± 1.15** | 31.6 ± 1.20** |

Note: the degree of reliability compared with the data of the control group * - Р < 0.05, ** - Р < 0.001

Table 2
Glutathione reductase activity in the blood serum of bulls in chronic cadmium toxicosis; (M ± m, n = 5)

| Time of blood test (days) | Glutathione reductase (nmol NADPH/min per 1 mg of protein) |
|--------------------------|----------------------------------------------------------|
|                          | Control | Animal Groups |
|                          |         | Experimental 1 | Experimental 2 |
| At the beginning of the experience | 1.60 ± 0.035 | 1.62 ± 0.043 | 1.61 ± 0.045 |
| First day                | 1.62 ± 0.040 | 1.75 ± 0.040* | 1.78 ± 0.038* |
| eighth day               | 1.60 ± 0.038 | 1.53 ± 0.038 | 1.53 ± 0.040 |
| sixteenth day            | 1.59 ± 0.041 | 1.38 ± 0.055* | 1.34 ± 0.058* |
| twenty fourth day        | 1.61 ± 0.044 | 1.31 ± 0.025** | 1.28 ± 0.025** |
| thirtieth day            | 1.60 ± 0.035 | 1.39 ± 0.040* | 1.35 ± 0.035** |

Note: the degree of reliability compared with the data of the control group * - Р < 0.05, ** - Р < 0.001

It is known that this enzyme catalyzes the reduction of lipid peroxide and the restoration of hydrogen peroxide to water, protecting the body from oxidative damage and in the long-term development of oxidative stress.

At the beginning of the experiment, the activity of glutathione reductase was within the limits of the physiological norm. Feeding of cadmium chloride to animals contributed to an increase in enzyme activity on the first day of both the first and second experimental groups, respectively, by 8 and 10%. In the distant, on the eighth day of the experiment, the enzyme activity decreased and on the sixteenth day of the experiment the activity of the enzyme in the first experimental group was 1.38 ± 0.055 nmol NADPH/min per 1 mg of protein, in the second experimental group 1.34 ± 0.058 nmol NADPH/min per 1 mg squirrel.

On the twentieth day of the experiment, the enzyme activity continued to decrease and in animals that were asked for cadmium chloride at a dose of 0.03 mg/kg of body weight, the activity was 1.31 ± 0.025 nmol NADPH/min per 1 mg of protein, and animals who were asked for cadmium chloride at a dose of 0.05 mg/kg of body weight, respectively, the enzyme activity was 1.28 ± 0.025 nmol NADPH/min per 1 mg of protein, compared with the values of the control group of animals, it decreased to 19 and 20%, respectively. On the thirtieth day of the experiment, a slight increase in the activity of glutathione reductase was noted; however, relative to the control group of animals, the activity of the enzyme remained low.

The activity of glucose-6-phosphate dehydrogenase in the blood of the experimental bulls is shown in Table 3. From these data it follows that at the beginning of the experiment the activity of the enzyme in the experimental groups of animals was within the limits of the physiological norm.

After ingestion of cadmium chloride in a dose of 0.03 mg/kg body weight into experimental animals, the activity of glucose-6-phosphate dehydrogenase in the blood of the experimental bulls is shown in Table 3. From these data it follows that at the beginning of the experiment the activity of the enzyme in the experimental groups of animals was within the limits of the physiological norm.

On the thirtieth day of the experiment, we note a slightly increased activity of glutathione peroxidase, however, compared with the control group, it remained at a low level.
membranes, participation in the metabolism of xenobiotics, protection against free radicals, support of the function of animals performs many functions, some of which are explained by the depletion of the glutathione system due to the formation of a large number of free radicals and lipid peroxidation processes.

The most important antioxidant of the glutathione antioxidant defense system is glutathione, which in the body of animals performs many functions, some of which are protection against free radicals, support of the function of membranes, participation in the metabolism of xenobiotics, influence on the activity of enzymes (Ferreira et al., 1999; Bielenichev et al., 2002). Glutathione has a direct antioxidant effect. Reduced glutathione acts as an electron donor to neutralize reactive oxygen species.

The level of reduced glutathione in bulls' blood by cadmium loading is given in Table 4. On the first day of the experiment, the level of reduced glutathione in the blood of animals who were fed with cadmium chloride at a dose of 0.03 mg/kg body weight was 34.17 ± 0.55 mg%, which is 5% more than the value of the control group of animals. On the eighth day of the experiment, the level of the indicator began to decline by 9% compared to the previous day of experience. On the sixteenth day of the experiment, the level of reduced glutathione continued to decrease and amounted to 30.28 ± 0.5 mg%, on the twenty-fourth day of the experiment, the level of the indicator was investigated, was 10% lower than the control group of animals. On the thirtieth day of the experiment, an increase in the level of reduced glutathione in the first experimental group of animals was noted.

After feeding cadmium chloride at a dose of 0.05 mg/kg of body weight, the level of reduced glutathione increased at the beginning of the experiment, but starting from eight days of the experiment, the indicator decreased to 29.95 ± 0.65 mg% on the sixteenth day. On the twenty-fourth day of the test, the level of reduced glutathione fluctuated within the same range as in the previous case. On the thirtieth day of the experiment, the level of glutathione began to increase, however, compared with the control group of animals, it was lower by 6%.
suppresses the activity of enzymes of the antioxidant system. As it is known, cadmium contributes to an increase in the content of reactive oxygen species in cells directly and indirectly. Reactive oxygen species induce lipid peroxidation and other processes leading to destructive changes in liver cells. Under such conditions, a decrease in the level of antioxidant protection of liver cells in animals intoxicated with cadmium may increase its harmful effects on the organism as a whole (Honskyy et al., 2001). Cadmium compounds have a high biological activity, they easily form complex compounds with proteins, nucleic acids than easily inactivate a number of enzymes. The most studied manifestation of the acute form of cadmium toxicosis in animals is the harmful effect on the functional state of the liver due to morphological and biochemical changes in hepatocytes after a single injection of the compounds of the above-mentioned element in doses exceeding 0.5–1.0 mg/kg body weight.

One of the features of the harmful effects of cadmium is its rapid absorption by the body and slow excretion, which leads to cumulation of this metal in the tissues (Lu et al., 2005). Cadmium accumulates mainly in the liver and kidneys and has a long half-life (up to 30 years), that is, in the applied aspect, it can be considered that for animals the deposition of cadmium in the body is lifelong.

Introduced intravenously or intraperitoneally, cadmium damages primarily the liver, and later on other organs (Hwang and Wang, 2001; Gupta et al., 2004). Cadmium toxicity is related to the ability of an element to induce the lipid peroxidation reaction of hepatocyte membranes (Watjen and Beyersman, 2004). In addition, the activity of certain enzymes, in particular glutathione peroxidase, glutathione reductase, glucose-6-phosphatase, is reduced, and it can be a test for early diagnosis of liver tissue damage (El-Shahat et al., 2009).

The literature data on the relationship between cadmium-induced damage to liver cells and the activity of the POL processes is also often contradictory. Some researchers believe that these phenomena are independent and the main destructive effect of the metal is associated only with a violation of the energy metabolism of hepatocytes (Antonio et al., 1998; El-Shahat et al., 2009; Al-Azemi et al., 2010). However, the vast majority of researchers believe that cadmium causes a significant increase in lipid peroxidation processes and a decrease in the activity of antioxidant enzymes: glutathione peroxidase, superoxide dismutase, catalase (El-Shahat et al., 2009; Al-Attar, 2011). It has been proven that cadmium activates PLO not only in parenchymal organs, but also in the tissues of the kidneys and brain (El-Refaï and Eissa, 2012). The administration of 3.3 mg/kg (0.05 DL50) cadmium chloride for 30 days changed the prooxidant-antioxidant status of the rat liver. In addition, a sharp increase in the content of diene conjugates was observed; under these conditions, the activity of glutathione peroxidase decreased significantly. The suppression of catalase, superoxide dismutase and glutathione peroxidase activity, as well as the content of vitamin E and ascorbic acid in the liver under the influence of cadmium has been found in other scientific works (Gupta et al., 2004).

1. Feeding cadmium chloride to bulls at doses of 0.03 and 0.05 mg/kg of body weight for 30 days led to the development of chronic cadmium toxicosis;
2. Feeding cadmium chloride to bulls at a dose of 0.05 mg/kg body weight resulted in a significant decrease in the non-enzyme and enzyme glutathione system of the bullock organisms’ antioxidant protection, as indicated by a decrease in their blood activity of glutathioneperoxidase, glutathionereductase, glucose-6-phosphate dehydrogenase and activity reduced glutathione.
3. The conducted studies allowed deeper disclosure of the pathogenesis of the toxic effect of cadmium on the body of bulls and use these data in the development of an antidote for cadmium intoxication.

Prospects for further research. The results of the research will be applied in the future to study the system of antioxidant protection and lipid peroxidation processes in the blood of bulls to develop an antidote preparation for treating animals with cadmium toxicosis.

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