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The effect of methionin, phenaron, and metiphen in different doses on the activity of the enzymatic link of the antioxidant protection of the piglets' bodies

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Abstract. Peroxidation of all lipids in the body is controlled by the system of antioxidant protection, which ensures the binding and modification of free radicals, preventing the formation or destruction of peroxides. We studied the effects of methionin, phenaron, and metiphen in appropriate doses on the activity of the enzymatic link of the antioxidant protection of the piglets' bodies. The research was conducted on 50 three-month-old piglets of the Large White Breed. The diet of the piglets was balanced in terms of nutrients and minerals. Based on the experimental studies, the correcting effect of methionin, phenaron, and metiphen on the activity of enzymes in the antioxidant defense system has been scientifically proven. In the piglets, the experimental drugs helped to increase the enzymatic link of the system of antioxidant protection: increase in the activity of superoxide dismutase, catalase, and glutathione peroxidase in the blood serum of the studied piglets. The highest indicators of the activity of the specified enzymes in the blood serum of the animals of the experimental groups were seen on the 30th, 60th, and 90th days of the experiment. It is worth noting that the experimental drugs showed better antioxidant properties in the appropriate doses: methionin at the dose of 4 mg/kg of body weight and phenaron at the dose of 1.20 mg/kg body weight. And metifen at the dose of 0.9 mg/kg of body weight. The use of methiphen in piglets contributed to a better antioxidant effect than phenaron and methionin separately. The components of metiphen act as synergists; therefore, they better strengthened the antioxidant protection of the piglets' bodies.

Keywords: antioxidants; enzymes; oxidative stress; phenosane acid; piglets.

Introduction

Each biological system reacts to the most minor toxic substances entering the environment. In this way, biological membranes play the role of natural boundaries of cells and organelles of the body (Ohorodnyk & Vishchur, 2015; Khariv et al., 2017; Angelova et al., 2021). They are the first to be negatively affected by toxicants (Martyshuk et al., 2018). Membrane pathology can be associated with malfunctioning of cell membrane proteins and modification of membrane lipids. Peroxidation of membrane phospholipids is one of the most common mechanisms of destruction of membrane structures (Ushkalov & Turko, 2016; Su et al., 2019; Jaganjac et al., 2021). Arachidonic, linoleic, and carboxylic acids can be the primary substrate of lipid peroxidation in cell membranes (Gaschler & Stockwell, 2017; Ramana et al., 2017). Due to the combination of oxygen, phospholipid molecules become more polarized. Therefore phospholipid hydroperoxides accumulate in the membrane layer, forming so-called peroxide clusters, which is one of the main ways of destroying the lipid part of membranes (Gutyj et al., 2022a, 2022b).

Peroxidation at almost all its stages forms many active products that result from the interaction of free radicals both among themselves and with biological macromolecules. Such products include peroxides, ketones, alcohols, aldehydes, dialdehydes that can interact with individual functional groups of proteins. This leads to their polymerization and destruction of amino-acid residues. They contain SH-, SCH_3-groups of cysteine, methionin, and NN-groups of lysine (Khomych et al., 2015; Usenko et al., 2020). Products of LPO are involved in the pathogenesis of well-known animal toxicosis and in implementing oxidative stress mechanisms through secondary activation (Ohorodnyk et al., 2013; Stoyanovskyy et al., 2020).

To ensure maximum protection from oxidative stress, cells have a well-developed antioxidant system containing various low- and high-molecular compounds that can "intercept" free radicals or neutralize their source. Antioxidants break molecular chains during reactions of free radical oxidation and destroy peroxide molecules.

The chain of antioxidant reactions in the mechanism of protective processes is the leading and most powerful, as they prevent not only the development of free radical reactions and the accumulation of peroxide anions and peroxides but also support high activity of redox processes, ensure the removal of terminal oxygen metabolites with their involvement in energy exchange and activation of synthesis processes (Pradeep et al., 2007; Ostapyuk et al., 2021). The proper functioning of the body's AOS is the key to the average life of pigs.

Therefore, we studied what effects methionin, phenaron, and metiphen in different doses have on the activity of the enzymatic link of the antioxidant protection of the body of intact piglets.

Material and methods

The study was conducted on 50 three-month-old piglets of the Large White Breed. We adhered to the rules that are mandatory when performing zootechnical experiments regarding selecting and maintai-

ning similar animals in groups. The diet of the piglets was balanced in terms of nutrients and minerals. The study was performed in accordance with the requirements of the European Convention on the Protection of Experimental Animals (86/609 EEC).

Ten groups were formed, with 5 animals in each: a control group and nine experimental groups. Piglets of group C were fed with the usual feed for the farm, which was balanced without adding the antioxidants mentioned above. Group E1 piglets were fed methionin in the dose of 2 mg/kg of body weight once daily with feed. Piglets of the E_2 group were fed methionin in the dose of 3 mg/kg of body weight once a day with feed. Group E_3 piglets were fed methionin in the dose of 4 mg/kg of body weight once a day with feed. Piglets of the E_4 group were fed phenaron in the dose of 1.10 mg/kg of body weight once a day with feed. Piglets of the E_5 group were fed phenaron with food in the dose of 1.15 mg/kg of body weight once a day. Piglets of the E_6 group were fed phenaron in the dose of 1.20 mg/kg of body weight once a day with feed. Piglets of the E_7 group were fed metiphen in the dose of 0.85 mg/kg of body weight once with feed. Piglets of the E_8 group were fed metiphen in the dose of 0.9 mg/kg body weight once a day with feed. Piglets of the E_9 group were fed metiphen in the dose of 0.95 mg/kg of body weight once a day with feed.

Methionin – Methioninum is a white crystalline powder with a specific smell and with the active substance content of at least 98.5%. It is well soluble in diluted mineral acids, caustic alkalis, and ammonia, and hardly soluble in water.

Phenaron is a complex compound containing 70% phenazanic acid and 30% zeolite. It dissolves poorly in cold water but better in hot water. Thermostable.

Metiphen – Metiphenum: white crystalline powder, with sweet taste and sulfur smell. It dissolves poorly in cold water, better in hot water (1:20). Thermostable. The drug contains phenaron and methionin.

The research results were analyzed using the Statistica 7.0 software package (StatSoft Inc., USA). Data are presented in the table as x ± SD (mean ± standard deviation). We used the Tukey's test to compare the difference in mean parameters between the control and experimental groups, where differences were considered statistically significant at $P < 0.05$ for all data.

Results

The activity of superoxide dismutase in blood serum of the intact piglets at the beginning of the research was within the range of 33.10–33.21 IU/min×mg of protein (Table 1). After feeding with methionin feed, the activity of SOD in blood serum of the piglets on the 10th day increased by 5.0% in group E_1 and by 5.1% in piglets of groups E_2 and E_3, compared with the indicator of control. On the 30th day, the activity of SOD in animals of the experimental groups continued to increase again, measuring 34.82 ± 0.19 IU/min×mg of protein in the animals that were fed methionin in the dose of 2 mg/kg of body weight and 34.85 ± 0.13 and 34.88 ± 0.12 IU/min×mg of protein in the animals fed methionin in doses of 3 and 4 mg/kg of body weight, respectively. On the 60th and 90th days of the experiment, the activity of SOD reached the highest value and fluctuated between 34.84 ± 0.05 and 34.92 ± 0.05 IU/min×mg of protein.

The study of the effect of methionin on the activity of SOD in blood of groups E_1, E_2, and E_3 revealed that methionin in the dose of 4 mg/kg of body weight promoted a better antioxidant effect than the use of this drug in smaller doses. Therefore, the higher the dose of methionin fed to the piglets, the higher was the activity of SOD in blood serum of the experimental piglets.

Intake of phenaron in the doses of 1.10, 1.15, and 1.20 mg/kg of body weight increased superoxide dismutase activity by 6.6% and 7.0% on the 10th day, respectively, compared with the control. On the 30th, 60th, and 90th days, the activity of SOD was slightly higher than the previous indicators. In the animals with fed phenaron in the doses of 1.10 and 1.15 mg/kg body weight, it increased to 35.40 ± 0.16 IU/min×mg of protein, and in the piglets fed with phenaron at a dose of 1.20 mg/kg body weight, SOD activity increased to 35.49 ± 0.05 IU/min×mg of protein.

Table 1

Effect of methionin, phenaron, and metiphen on the activity of superoxide dismutase in blood serum of intact piglets (IU/min×mg of protein, x ± SD, n = 5)

Groups	Study periods				
	at the beginning	10th day	30th day	60th day	90th day
C	33.11 ± 0.11^a	33.14 ± 0.17^a	33.26 ± 0.17^a	33.56 ± 0.05^a	33.69 ± 0.15^a
E_1	33.16 ± 0.16^a	34.79 ± 0.05^b	34.82 ± 0.19^b	34.84 ± 0.05^b	34.85 ± 0.06^b
E_2	33.13 ± 0.18^a	34.83 ± 0.21^b	34.85 ± 0.13^b	34.87 ± 0.06^b	34.89 ± 0.15^b
E_3	33.10 ± 0.14^a	34.83 ± 0.06^b	34.88 ± 0.12^b	34.91 ± 0.06^b	34.92 ± 0.05^b
E_4	33.16 ± 0.14^a	35.34 ± 0.13^c	35.34 ± 0.14^c	35.38 ± 0.13^c	35.40 ± 0.16^c
E_5	33.21 ± 0.16^a	35.34 ± 0.20^c	35.37 ± 0.05^c	35.40 ± 0.18^c	35.40 ± 0.17^c
E_6	33.14 ± 0.12^a	35.45 ± 0.22^c	35.47 ± 0.15^c	35.48 ± 0.04^c	35.49 ± 0.05^c
E_7	33.18 ± 0.13^a	35.96 ± 0.18^c	35.98 ± 0.16^d	36.06 ± 0.18^d	36.07 ± 0.19^d
E_8	33.10 ± 0.14^a	35.97 ± 0.14^c	36.04 ± 0.13^d	36.08 ± 0.14^d	36.10 ± 0.17^d
E_9	33.13 ± 0.12^a	35.97 ± 0.19^c	36.01 ± 0.12^d	36.05 ± 0.15^d	36.05 ± 0.12^d

Note: different letters in the column indicate that the samples of data significantly ($P < 0.05$) differ one from another according to the results of the Tukey test with the Bonferroni's Correction.

Therefore, feeding the piglets with phenaron increased the superoxide dismutase activity throughout the study. It should be noted that for the effective correction of SOD activity in blood serum of the piglets, the optimal dose of phenaron was used, in particular 1.20 mg/kg of body weight.

With the combined use of methionin and phenaron in the complex drug metifen, we saw the highest SOD activity in blood serum of the piglets throughout the experiment, compared with the use of these drugs separately. As can be seen in the data in Table 1, the activity of SOD in blood serum of animals of groups E_7, E_8, and E_9 on the 10th day increased by 8.5% compared with the control. In the following days of the experiment, the activity of SOD increased. Still, it was the highest in animals of the group that had consumed metiphen in the dose of 0.9 mg/kg of body weight. Therefore, it was 36.04 ± 0.13 IU/min×mg of protein on the 30th day, 36.08 ± 0.14 IU/min×mg of protein on the 60th day, and 36.10 ± 0.17 IU /min×mg of protein on the 90th day.

The activity of catalase in blood serum of the piglets at the beginning of the research in all animals of the experimental groups was within the limits of physiological indicators, ranging 1.21 ± 0.06 to 1.25 ± 0.06 nmol/min×mg of protein (Table 2). Intake of methionin feed increased the catalase activity in blood serum by 5.8% on the 10th day in animals of group E_1 and by 6.6% in piglets of animal groups E_2 and E_3. On the 30th day, catalase activity reached 1.29–1.30 nmol/min×mg of protein. On the 60th and 90th days, the highest activity of this enzyme was seen. In the animals that had consumed methionin in the dose of 2 and 3 mg/kg of body weight, the activity of catalase increased by 4.8%, respectively, whereas in the animals that had consumed methionin in the dose of 4 mg/kg, enzyme activity increased by 5.6%.

Therefore, methionin in the dose of 4 mg/kg of body weight caused the highest increase in catalase activity in blood serum, measuring 1.32 ± 0.05 nmol/min×mg of protein.

Phenaron in the piglets also increased catalase activity when consuming methionin, but the enzyme activity was slightly higher. Thus, on the 10th day, the activity of the enzyme increased by 9.1% and 10.7% in blood serum of animals of groups E_4, E_5, and E_6. Subsequently, the activity of catalase continued to increase. On the 30th day, it was 1.33 ± 0.07 nmol/min×mg protein in groups E_4 and E_5, and 1.35 ± 0.02 nmol/min in animals of group E_6 × mg of protein. On the 60th and 90th days, the activity of catalase in animals of the experimental groups remained at the same level. It was the highest in the group where animals consumed phenaron in the dose of 1.20 mg/kg of body weight, whereas relative to the control, it increased by 9.7%.

Table 2
Effect of methionin, phenaron, and metiphen on catalase activity in blood serum of piglets (nmol/min × mg of protein, x ± SD, n = 5)

Groups	Study periods				
	at the beginning	10th day	30th day	60th day	90th day
C	1.21 ± 0.06^{a}	1.21 ± 0.04^{a}	1.21 ± 0.05^{a}	1.24 ± 0.04^{a}	1.25 ± 0.06^{a}
E_1	1.24 ± 0.04^{a}	1.28 ± 0.08^{b}	1.29 ± 0.07^{b}	1.30 ± 0.06^{b}	1.31 ± 0.06^{b}
E_2	1.23 ± 0.06^{a}	1.29 ± 0.06^{b}	1.30 ± 0.08^{b}	1.30 ± 0.08^{b}	1.31 ± 0.07^{b}
E_3	1.21 ± 0.05^{a}	1.29 ± 0.05^{b}	1.30 ± 0.02^{b}	1.31 ± 0.05^{b}	1.32 ± 0.05^{b}
E_4	1.22 ± 0.04^{a}	1.32 ± 0.06^{bc}	1.33 ± 0.05^{bc}	1.34 ± 0.05^{bc}	1.35 ± 0.08^{bc}
E_5	1.24 ± 0.04^{a}	1.32 ± 0.05^{bc}	1.33 ± 0.07^{bc}	1.35 ± 0.08^{bc}	1.35 ± 0.03^{bc}
E_6	1.25 ± 0.06^{a}	1.34 ± 0.07^{bc}	1.35 ± 0.02^{bc}	1.36 ± 0.05^{bc}	1.36 ± 0.06^{bc}
E_7	1.21 ± 0.04^{a}	1.38 ± 0.02^{c}	1.38 ± 0.05^{c}	1.39 ± 0.07^{c}	1.39 ± 0.05^{c}
E_8	1.23 ± 0.05^{a}	1.39 ± 0.02^{c}	1.39 ± 0.06^{c}	1.40 ± 0.08^{c}	1.41 ± 0.02^{c}
E_9	1.22 ± 0.06^{a}	1.38 ± 0.05^{c}	1.39 ± 0.07^{c}	1.39 ± 0.05^{c}	1.40 ± 0.07^{c}

Note: see Table 1.

Intake of metiphen feed caused increase in the activity of catalase in the experimental piglets on the 10th day. Compared with the control, the activity of enzyme increased by 14.0% in piglets of groups E_7 and E_9 and by 14.9% in group E_8. On the 30th day, catalase activity remained at the same level as on the previous day of the experiment. On the 90th day, catalase activity was the highest in the animals that consumed methiphen. In animals of the group that received methiphene in the dose of 0.85 mg/kg of body weight, the enzyme activity was 1.39 ± 0.05 nmol/min×mg of protein, and in those were fed with metifen in the dose of 0.9 mg/kg body weight, enzyme activity was 1.41 ± 0.02 nmol/min×mg of protein. The enzyme activity was somewhat lower in animals of experimental group E_9, i.e., which had consumed metifen in the dose of 1.0 mg/kg body weight. It accounted for 1.40 ± 0.07 nmol/min×mg of protein.

As can be seen in the data in Table 3, the activity of glutathione peroxidase at the beginning of the study in animals of all experimental groups fluctuated within the range of 35.48–35.53 nmol/min×mg of protein. After feeding piglets with methionin, the activity of HPO in their blood serum increased during the experiment. In addition, it reached its highest activity on the 90th day. It was 35.72 ± 0.18 nmol/min×mg of protein in animals of experimental group E_1, 35.73 ± 0.13 nmol/min×mg of protein in animals of group E_2, and 35.74 ± 0.12 nmol/min×mg of protein in animals of group E_3, whereas equaling 35.52 ± 0.21 nmol/min×mg of protein in animals of the control group.

Comparing the data on indicators of glutathione peroxidase activity in piglets of experimental groups E_4, E_5, and E_6 with the indicators of the control group of animals, we determined their increase, the degree of which depended on effect of the drug in the appropriate dose. Therefore, on the 90th day of the experiment, the activity of glutathione peroxidase in animals fed with phenaron in the dose dose of 1.10 mg/kg body weight was 35.92 ± 0.15 nmol/min×mg of protein, and in the animals that consumed phenaron in doses of 1.15 and 1.20 mg/kg body weight, it was 35.94 ± 0.04 and 35.96 ± 0.21 nmol/min×mg of protein, respectively.

Table 3
The effect of methionin, phenaron, and metiphen on the activity of glutathione peroxidase in piglet erythrocytes (nmol/min × mg of protein, x ± SD, n = 5)

Groups	Study periods				
	at the beginning	10th day	30th day	60th day	90th day
C	35.49 ± 0.17^{a}	35.48 ± 0.16^{a}	35.50 ± 0.18^{a}	35.51 ± 0.12^{a}	35.52 ± 0.21^{a}
E_1	35.50 ± 0.16^{a}	35.67 ± 0.19^{a}	35.69 ± 0.05^{a}	35.71 ± 0.20^{ab}	35.72 ± 0.18^{ab}
E_2	35.48 ± 0.14^{a}	35.70 ± 0.05^{ab}	35.71 ± 0.22^{ab}	35.72 ± 0.07^{ab}	35.73 ± 0.13^{ab}
E_3	35.53 ± 0.17^{a}	35.71 ± 0.14^{ab}	35.73 ± 0.12^{ab}	35.73 ± 0.22^{ab}	35.74 ± 0.12^{ab}
E_4	35.51 ± 0.18^{a}	35.87 ± 0.15^{ab}	35.89 ± 0.14^{ab}	35.91 ± 0.21^{ab}	35.92 ± 0.15^{ab}
E_5	35.49 ± 0.16^{a}	35.88 ± 0.15^{ab}	35.90 ± 0.07^{ab}	35.93 ± 0.14^{ab}	35.94 ± 0.04^{ab}
E_6	35.52 ± 0.19^{a}	35.90 ± 0.16^{ab}	35.91 ± 0.18^{ab}	35.93 ± 0.14^{ab}	35.96 ± 0.21^{ab}
E_7	35.50 ± 0.15^{a}	36.09 ± 0.17^{b}	36.11 ± 0.13^{b}	36.12 ± 0.13^{b}	36.13 ± 0.14^{b}
E_8	35.51 ± 0.06^{a}	36.11 ± 0.06^{b}	36.12 ± 0.14^{b}	36.15 ± 0.12^{b}	36.15 ± 0.17^{b}
E_9	35.53 ± 0.15^{a}	36.11 ± 0.14^{b}	36.12 ± 0.15^{b}	36.13 ± 0.14^{b}	36.14 ± 0.16^{b}

Note: see Table 1.

Analyzing the data on changes in the activity of glutathione peroxidase in blood serum of the experimental animals that had consumed metiphen, we determined that the dose of 0.9 mg/kg body weight increased the activity of the studied enzyme by 2% on the 10th day, and on the 60th and 90th days the activity of glutathione peroxidase increased to 36.15 ± 0.17 nmol/min×mg of protein.

Discussion

The antioxidant properties of the drugs we used in our work on the intact piglets were studied by indicators such as superoxide dismutase, catalase, and glutathione peroxidase activity (Leskiv et al., 2020; Gutyj et al., 2023). It is known that superoxide dismutase is represented by a family of metalloenzymes that catalyze the dismutation reaction of superoxide radicals. It is characterized by extreme structural stability and is one of the most thermostable globular proteins (Bashchenko et al., 2020). Catalase is one of the primary antioxidants of the defense system, which is closely related to the activity of superoxide dismutase. This enzyme belongs to the oxidoreductase class. It is a chromoprotein consisting of four identical subunits with the molecular weight of 62,000. It decomposes hydrogen peroxide, formed in biological oxidation, into water and molecular oxygen ($2H_2O_2 \rightarrow 2H_2O + O_2$). In addition, hydrogen peroxide oxidizes low-molecular alcohols and nitrites in the presence of hydrogen peroxide, essential in developing nitrate-nitrite toxicosis. It also participates in tissue respiration (Chernushkin et al., 2016; Yan & Spaulding, 2020; Liu et al., 2022; Chen et al., 2023).

Based on the conducted studies, use of the antioxidant preparations (methionin, phenaron, and metiphen) increased the activity of two main enzymes of the body's antioxidant defense in the blood serum of the experimental piglets: superoxide dismutase and catalase. Increasing the activity of these enzymes in blood of the piglets prevented the increase of free radical oxidation of lipids and the development of the so-called oxidative stress in piglets.

Glutathione peroxidase is one of the main enzymes that destroys reactive oxygen species (ROS). Under certain conditions, increasing the intensity of ROS formation over the speed of their detoxification can lead to cell damage (Slobodian et al., 2021; Flohé et al., 2022; Lai et al., 2023). With severe or prolonged stress, the concentration of ROS in the cell can increase, and, starting from a certain threshold level of these compounds, the mobilization of the cell's defense systems weakens, and the processes that causes apoptosis or necrosis are activated (Verveha et al., 2023). That is why it is important to study how those drugs affect the activity of glutathione peroxidase in blood of piglets. Relative normalization of the analyzed parameter was seen in the piglets fed with methionin and phenaron. However, in piglets that received metifen with feed, a significant normalization of glutathione peroxidase activity was noted, which was confirmed by high antioxidant activity.

Conclusions

The use of methionin, phenaron, and metiphen in piglets promoted the activation of the enzyme system of antioxidant protection, evidenced in increase in the activity of superoxide dismutase, catalase, and glutathione peroxidase in blood serum of the studied piglets.

The best antioxidant effect was manifested when the piglets consumed methionin in the dose of 4 mg/kg of body weight, phenaron in 1.20 mg/kg of body weight, and metifen in 0.9 mg/kg.

The highest activity of enzymes of the antioxidant protection system in blood of animals of the experimental groups was observed on the 30th, 60th, and 90th days of the experiment.

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