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The influence of “Butaselmavit” on the antioxidant status of the cows' organisms during the development of endotoxycosis

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It is known that the occurrence of intoxication accompanies many diseases in pregnant animals. One of the causes of internal intoxication is inadequate feeding of pregnant cows. It is important to note that pregnant cows' feeding and maintenance conditions significantly affect their future offspring's health. Modern understanding of the mechanism of action of endotoxins on the body of pregnant cows is based on the leading role of the antioxidant system in it. The work aimed to study the effect of the liposomal preparation “Butaselmavit” on the antioxidant status of the cows' organisms during the development of endotoxycosis. The experiments were conducted on pregnant cows of the Ukrainian black-and-white dairy breed. Two groups of animals were formed, with 5 pregnant cows in each: control and experimental. The cows in the control group (C) had characteristic clinical signs of endotoxycosis. The cows in the experimental group (E) were administered “Butaselmavit” at 10 ml per animal doses in the eighth and ninth months of gestation. Our studies showed that pregnant cows with clinical signs of endotoxycosis exhibited significant changes in the body's antioxidant defense system activity. The research results indicate that the activity of enzymes in the glutathione antioxidant defense system significantly decreases in the 8th and 9th months of gestation. The reduced activity of antioxidant enzymes is caused by the accumulation of lipid peroxidation (LPO) products that inhibit the activity of these enzymes. The use of “Butaselmavit” in cows during the development of endotoxycosis contributes to the suppression of lipid peroxidation processes, as indicated by the low levels of lipid hydroperoxides and TBC-active products. When the liposomal preparation “Butaselmavit” was used in pregnant cows with endotoxycosis, activation of the antioxidant defense system was also observed. This indicates a high level of activity of the enzymes in the glutathione defense system, namely an increase in the activity of glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase. This is likely related to direct and indirect antioxidants in the liposomal preparation, which interact with each other, inhibiting the formation of free radicals and lipid oxidation processes.

Key words: endotoxycosis, fattening cows, antioxidants, reactive oxygen species, lipid peroxidation.

Вплив “Бутаселмевіту” на антиоксидантний статус організму корів за розвитку ендотоксикозу

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Відомо, що багато хвороб у вагітних тварин супроводжуються виникненням інтоксикації. Однією з причин виникнення внутрішньої інтоксикації є неповноцінна годівля тільних корів. Важливо зауважити, що умови годівлі та утримання тільних корів значно впливають на здоров'я їхнього майбутнього потомства. Сучасні уявлення про механізм дії ендотоксинів на організм тільних корів ґрунтуються на провідній ролі в ньому антиоксидантної системи. Метою роботи було дослідити вплив ліпосомального препарату “Бутаселмевіт” на антиоксидантний статус організму корів за розвитку ендотоксикозу. Досліди проводили на тільних коровах української чорно-рябої молочної породи. Було сформовано дві групи тварин по 5 тільних корів у кожній: контрольну і дослідну. Корови контрольної групи (К) мали характерні клінічні ознаки ендотоксикозу. Тваринам дослідної групи (Д) застосовували “Бутаселмевіт” у дозі 10 мл/тварину на восьмому і дев'ятому місяці тільності. Як показали результати наших досліджень, у тільних корів, у яких були клінічні ознаки ендотоксикозу, встановлені вірогідні зміни активності системи антиоксидантного захисту організму. Результати досліджень вказують на те, що активність ензимів глутатіонової системи антиоксидантного захисту вірогідно знижується на 8-ому і 9-ому місяцях тільності. Знижена активність ензимів-антиоксидантів зумовлена нагромадженням продуктів ПОЛ, що пригнічують активність даних ензимів. Застосування коровам за розвитку ендотоксикозу препарату “Бутаселмевіту” сприяє пригніченню процесів пероксидного окиснення ліпідів, на що вказує низький рівень гідроперексидів ліпідів та ТБК-активних продуктів. При використанні ліпосомального препарату “Бутаселмевіт” у тільних корів за ендотоксикозу спостерігалася також активація системи антиоксидантного захисту, а саме підвищення активності глутатіонпероксидази, глутатіонредуктази та глюкозо-6-фосфатдегідрогенази. Ймовірно, це пов'язано з наявністю прямих і непрямих антиоксидантів у складі ліпосомального препарату, які взаємодіють між собою, пригнічуючи утворення вільних радикалів та процеси окиснення ліпідів.

Ключові слова: ендотоксикоз, тільні корови, антиоксиданти, активні форми кисню, пероксидне окиснення ліпідів.

Introduction

According to literary sources, pregnant cows' feeding and maintenance conditions significantly affect their offspring's future (Bomko et al., 2018; Denkovich et al., 2021; Bashchenko et al., 2021; 2023; Sidashova et al., 2024). Therefore, a cow must receive adequate nutrients from the beginning of pregnancy for health, fetal development, and milk production. A deficiency or excess of energy and biologically active substances in the diet can cause metabolic disorders in pregnant cows (Borshch et al., 2020; 2021; Mylostyvyi et al., 2021; 2024; Klimkovetskaya et al., 2024).

During the development of endotoxemia in animals, dystrophic processes in the placenta and impaired microcirculation in this organ are observed. According to Levchenko V.I. (Levchenko et al., 2005), endotoxemia in high-yielding cows leads to liver dysfunction, causing the accumulation of a significant amount of toxic metabolites. These substances increase kidney workload and contribute to the development of hepatorenal syndrome. Excessive accumulation of ketone bodies in high-yielding cows can cause complications in the central nervous system (Hrymak, 2015; Grymak et al., 2020; Lozynskyi et al., 2023).

A characteristic feature of endotoxemia in pregnant cows is the disruption of the albumin-to-globulin ratio. Studies have shown that a decrease in animal albumin

levels leads to fat metabolism disorders and the development of fatty liver dystrophy. Low albumin levels also affect plasma's transport and detoxification functions (Boosman et al., 1991; Kraievskyi, 2000; Zaviyukha et al., 2009; Broda et al., 2013).

It has also been recorded that endogenous intoxication in animals leads to the development of stress (Clark et al., 1991; Andersen, 2003; Shcherba & Korda, 2019). In farm animals, two hormones are produced during stress: adrenaline and cortisol. They contribute to increased heart rate and respiratory movements and suppress the immune system. Stress also negatively affects reproductive function, reducing the production of sex hormones and contributing to the development of cardiovascular diseases (Culbertson & Osburn, 1980; Chabanenko et al., 2024).

Several vital biochemical mechanisms are involved in developing endotoxemia in cattle, one of which is the activation of free radical oxidation processes. Since pregnancy in animals is a physiological state that requires significant energy for biosynthesis and a greater volume of oxygen, it is characterized by increased cellular respiration and, as a result, oxidative stress. The entire period of cow pregnancy, as noted in the literature review, is accompanied by the activation of lipid peroxidation (LPO) (Eades, 1993; Chala & Rusak, 2016; Slivinska et al., 2021).

The intensity of free radical processes in cows depends on the amount of oxygen in their tissues and the

activity of protective systems, which consist of enzymes and other defense mechanisms (Gutyj et al., 2016; 2017; 2018). Excessive accumulation of free radicals and reactive oxygen species in cows' bodies can lead to oxidative stress, which can cause the development of endotoxemia. The antioxidant defense system of the animal body, which regulates lipid peroxidation reactions in cellular structures, is an essential mechanism for preventing damage caused by free radicals and peroxide compounds in normally functioning systems (Martyshuk et al., 2016; Martyshuk & Hutyi, 2021).

The aim of the study

The work aimed to investigate the effect of the liposomal drug "Butaselmavit" on the antioxidant status of the organism of cows during the development of endotoxemia.

Material and methods

The experiments were carried out in the laboratory of the Department of Hygiene, Sanitation, and General Veterinary Prevention named after M. V. Demchuk, Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv, and FE "Mezhyrichia" (Zarichia village, Lviv region).

The experiments were conducted on pregnant cows of the Ukrainian black-and-white dairy breed. Two groups of animals were formed, with 5 pregnant cows in each: control and experimental. The cows in the control group (C) had characteristic clinical signs of endotoxemia. The cows in the experimental group (E) were administered "Butaselmavit" at 10 ml per animal doses in the eighth and ninth months of gestation.

Blood for biochemical studies was collected from the jugular veins of the animals in the 8th and 9th months of gestation.

In the blood serum, the activity of glutathione peroxidase (GP) and glutathione reductase (GR) was studied using the method of V. V. Lemeshko (Vlizlo, 2012); glucose-6-phosphate dehydrogenase (G-6-PDH) using the method of N. Z. Baquezetal (Vlizlo, 2012); the level of TBC-active products using the method of E. N. Korobeynikov (Vlizlo, 2012); and the lipid hydroperoxides (LHP) content using the method described by V.V. Mironchuk (Vlizlo, 2012).

The numerical values of the hematological and biochemical blood indicators obtained were expressed in international units. The research results were subjected to biometric analysis using mathematical statistics methods accepted in biology and medicine, using the Microsoft Excel program ("Statistica 5.0", "Statgraphica", "Biostat"). The degree of significance compared to the control group's data was determined – $P < 0.05$ – *, $P < 0.01$ – **, $P < 0.001$ – ***.

Results and discussion

The antioxidant effect largely depends on the glutathione defense system, including glutathione, glutathione

peroxidase, reductase, glucose-6-phosphate dehydrogenase, and other components.

According to Fig. 1a, the lowest activity of glutathione peroxidase was in cows of the control group, which showed clinical signs of endotoxemia. Thus, in the 8th month of gestation, the activity in the blood of intoxicated cows was 20.1 ± 1.05 nmol GSH/min/mg protein; in the 9th month, it was 19.4 ± 1.19 nmol GSH/min/mg protein. The use of "Butaselmavit" in the experimental animals contributed to an increase in the activity of this enzyme in the blood serum of the experimental group by 26.9 % in the 8th month of gestation and by 40.7 % in the 9th month compared to the control group cows.

In addition to the activity of glutathione peroxidase, studying the activity of glutathione reductase is essential, as these two enzymes are involved in the oxidation and reduction of glutathione. When studying the activity of glutathione reductase, it was found that in the blood of the control group cows, it was the lowest, with the enzyme activity decreasing by 16 % in the 9th month of gestation compared to the initial values (Fig. 1b). In the experimental group of cows, an increase in enzyme activity was observed, with glutathione reductase activity increasing by 24 % in the 8th month of gestation and by 81 % in the 9th month of gestation compared to the control group (C).

To study the impact of endotoxemia in cows on glucose catabolism in erythrocytes, the activity of the enzyme glucose-6-phosphate dehydrogenase (G-6-PDH), which catalyzes the first stage of the pentose phosphate pathway, was analyzed. Glucose is the primary energy source for erythroid cells in the blood, and the intermediate products of its catabolism affect oxygen transport by hemoglobin. Therefore, the dynamics of this enzyme in the blood allow assessing the level of energy supply to erythrocytes and other aspects of their functional activity.

Research results indicate a decrease in glucose-6-phosphate dehydrogenase activity in the blood of cows in the control group during the development of endotoxemia (Fig. 1c). This indicator decreased over a long period, reaching a value of 58.4 ± 2.74 nmol NADPH/min/mg protein in the 9th month of gestation.

Glucose-6-phosphate dehydrogenase plays a crucial role in converting monosaccharides in the pentose phosphate pathway, which is closely linked with the functioning of the glutathione system. This metabolic pathway promotes the formation of NADPH, a cofactor for glutathione reductase, an essential enzyme in the antioxidant system.

Thus, the obtained results, indicating the suppression of glucose-6-phosphate dehydrogenase, show a decrease in the activity of glucose catabolism through the pentose phosphate pathway. This also indicates a reduction in the intensity of NADP regeneration in the erythrocytes of animals during the development of endotoxemia. The observed effect may likely disrupt the antioxidant defense system's metabolism and erythrocytes' functional characteristics.

The use of the "Butaselmavit" preparation in cows under conditions of developing endotoxemia led to an increase in the activity of the glucose-6-phosphate dehydrogenase enzyme throughout the study period. Compared to the control group animals that did not receive the

experimental preparation, the enzyme activity increased by 9.8 % in the 8th month of gestation, reaching a level of 66.6 ± 2.67 nmol NADPH/min/mg protein in the 9th month of gestation.

Thus, the use of “Butaselmavit” contributed to an increase in the activity of the enzymatic glutathione system, which is part of the cow's antioxidant defense. This prevents the development of oxidative stress, which occurs during endotoxemia in pregnant cows.

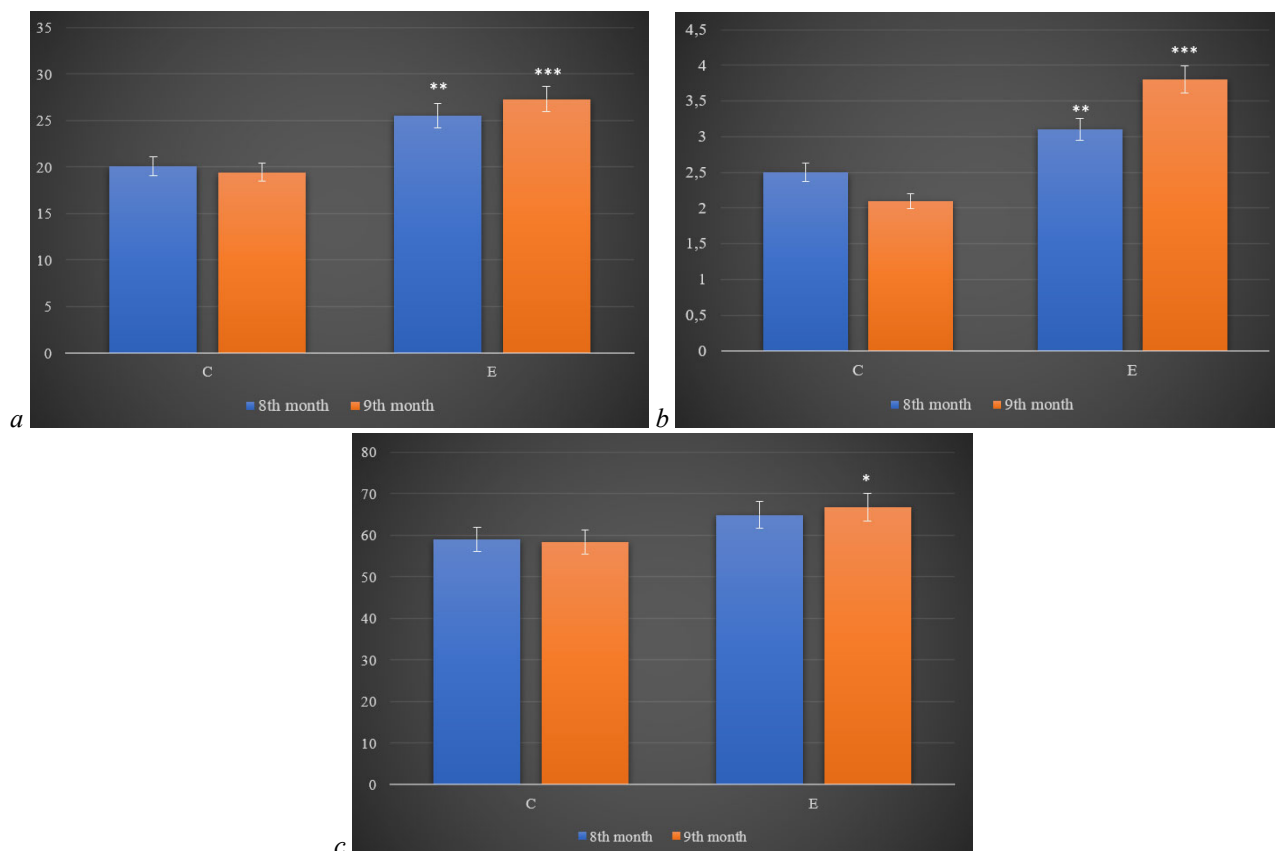


Fig. 1. The influence of “Butaselmavit” on the activity of the glutathione system in the body of cows during the development of endotoxemia: *a* – glutathione peroxidase, nmol GSH/min/mg proteins; *b* – glutathione reductase, nmol NADPH/min/mg proteins; *c* – glucose-6-phosphate-dehydrogenase, nmol NADPH/min/mg proteins ($M \pm m$, $n = 5$)

Our studies also showed the development of oxidative stress in the blood of pregnant cows. The physiological state of uncomplicated pregnancy in animals requires significant energy expenditure for biosynthetic processes and needs a greater volume of oxygen, which leads to enhanced cellular respiration. As evidenced by data from scientific literature, this results in oxidative stress throughout the entire period of cow pregnancy.

Disruption of the internal environment balance caused by oxidative stress and low adaptability of animals contributes to the development of a hypoxic state. This activates neuroendocrine reactions that lead to metabolic process disorders in the bodies of pregnant cows. Primary products of oxidative stress, including hydroperoxides, are unstable compounds and can lead to the formation of stable secondary products, among which TBC-active components are significant.

Initial products of lipid peroxidation (LPO) – hydroperoxides – are unstable substances that undergo further oxidation, forming more stable secondary products.

Among them, TBC-active products are particularly significant.

Monitoring the course of lipid peroxidation processes showed that in cows of group C, the level of lipid hydroperoxides in their blood during the 8th and 9th months of gestation was high (Fig. 2a). It is worth noting that it reached its highest level in the 9th month of gestation, which amounted to $411.2 \pm 12.86 E \times 1000/cm^3$ in the blood of control group cows.

The level of intermediate lipid peroxidation products in the blood of control group cows was 5.7 ± 0.20 nmol/cm³ in the 8th month of gestation and 6.4 ± 0.23 nmol/cm³ in the 9th month of gestation.

The increase in TBC-active products indicates the activation of peroxidation processes. The detected changes in these processes suggest a possible shift in the intrauterine programming of systems regulating the main stages of this process, particularly the supply of substrate (free fatty acids) and the effectiveness of the antioxidant defense system.

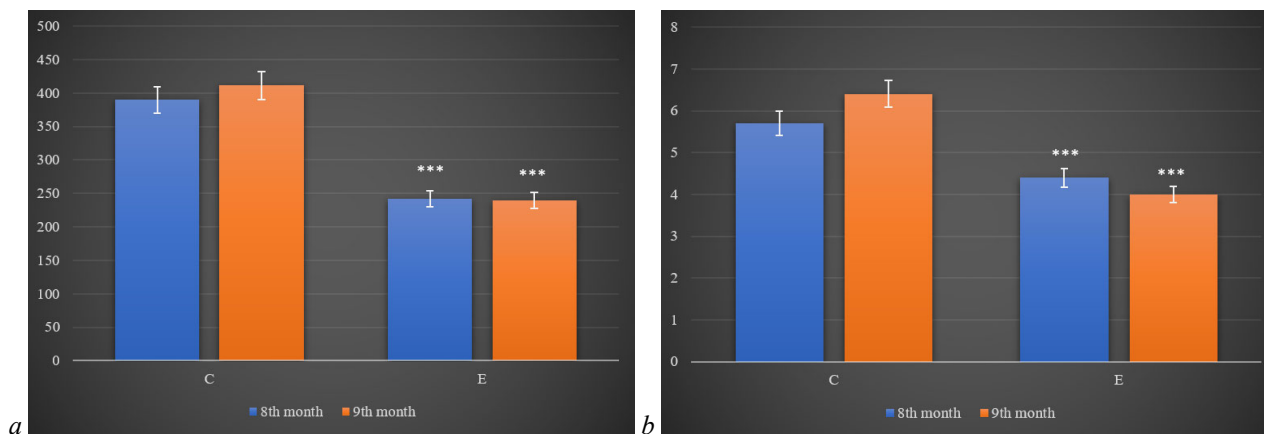


Fig. 2. The effect of “Butaselmavit” on the level of lipid peroxidation products in the blood of cows during the development of endotoxemia: a – hydroperoxides of lipids, E × 1000/cm³; b – TBC-active products, nmol/cm³ (M ± m, n = 5)

The parenteral administration of the liposomal preparation “Butaselmavit” to cows in the experimental group significantly reduced, compared to cows in the control group C, the levels of lipid hydroperoxides and TBC-active products in the blood during the 8th and 9th months of gestation. Specifically, the level of lipid hydroperoxides in the blood of the experimental group E decreased by 38 % in the 8th month of gestation, and the level of TBC-active products decreased by 22.8 % compared to the control. In the 9th month of gestation, the lowest levels of primary and intermediate products of lipid peroxidation were observed, amounting to $239.2 \pm 11.67 \text{ E} \times 1000/\text{cm}^3$ (lipid hydroperoxides) and $4.0 \pm 0.20 \text{ nmol}/\text{cm}^3$ (TBC-active products), respectively (Fig. 2b).

These data indicate that administering “Butaselmavit” to cows increases the activity of the blood antioxidant system and can effectively reduce the level of lipid peroxidation products. Under conditions of stress caused by endotoxemia, this positively affects the organism's physiological properties.

Conclusions

The application of the liposomal preparation “Butaselmavit” to cows with the development of endotoxemia contributed to the increase in the enzymatic activity of the antioxidant defense system, as indicated by the increased activity of glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase.

The use of Butaselmavit in cows with the development of endotoxemia helps to inhibit lipid peroxidation processes, as indicated by the low level of lipid hydroperoxides and TBC-active products.

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Conflict of interest

The authors declare that there is no conflict of interest.

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