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Chelate compounds and their use for correction of trace element deficiencies in livestock (review)

Andrey G. Koshchaev, Natalya E. Gorkovenko, Anastasia V. Kosykh, Darya V. Antipova
Kuban State Agrarian University named after I. T. Trubilin, 13 Kalinina str., Krasnodar 350044, Russia

ABSTRACT

Livestock and poultry diseases occurring due to mineral or vitamin deficiencies are widely reported and belong to the factors restraining the development of livestock industry. Almost until the 90s of the last century, the conditions associated with trace element deficiency were prevented and treated using inorganic compounds. In recent decades, scientists have synthesized chelate metal compounds using organic carriers, determining the high bioavailability of these compounds and the efficiency that repeatedly exceeds the efficiency of inorganic compounds. Amino acids are preferably used as organic carriers. In addition to their main function, i.e. replenishing the trace element deficiency, chelate compounds increase the enzymatic activity, the functional activity of the immune system, and are also able to enhance the absorption of other trace elements, showing a synergistic effect. Due to the immunostimulatory activity resulting from increase in the content of sialic acids, properdin, ceruloplasmin, gamma globulin protein fraction, the metal chelates (copper, cobalt, iodine) can be used as immune response modulators. Iron chelate compounds are used for therapy and prevention of iron deficiency anemias not only in veterinary, but also in human medicine. This paper is based on data analysis of Scopus, CyberLeninka, PubMed, RSCI and other databases and systematizes scientific knowledge on the problem of designing and synthesizing metal chelate compounds using organic carriers. The scientific rationale is given for the use of amino acids and organic acids as organic carriers of metal, vitamin and other compounds. The mechanism of biological action of chelate compounds and the pathogenesis of trace element deficiencies in animals are considered, while the advantages of chelate compound use in microelementoses therapy and prevention are specified.

Keywords: review, chelate compounds, organic carriers, biological action, iron deficiency anemia, pathogenesis, prevention, treatment

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For correspondence: Natalya E. Gorkovenko, Dr. Sci. (Biology), Associate Professor, Professor of the Department of Microbiology, Epizootology and Virology, Kuban State Agrarian University named after I. T. Trubilin, 13 Kalinina str., Krasnodar 350044, Russia, *e-mail: gorkovenko.n@kubsau.ru*

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Хелатные соединения и их использование для коррекции микроэлементозов сельскохозяйственных животных (обзор литературы)

А. Г. Кощаев, Н. Е. Горковенко, А. В. Косых, Д. В. Антипова
ФГБОУ ВО «Кубанский государственный аграрный университет имени И. Т. Трубилина» (ФГБОУ ВО Кубанский ГАУ), ул. им. Калинина, 13, г. Краснодар, 350044, Россия

РЕЗЮМЕ

Болезни сельскохозяйственных животных и птиц, обусловленные дефицитом минеральных компонентов и витаминов, регистрируются повсеместно и являются одним из факторов, сдерживающих развитие животноводческой отрасли. Профилактика и лечение болезней, связанных с недостатком микроэлементов, практически до 90-х годов прошлого столетия осуществлялись с использованием неорганических соединений. В последние десятилетия учеными синтезированы хелатные соединения металлов с использованием органических носителей, что обусловливает их высокую биодоступность и эффективность, многократно превосходящую эффективность неорганических форм. В качестве органических носителей предпочтительное использование получили аминокислоты. Хелатные соединения, кроме своей основной функции восполнения дефицита микроэлементов, повышают активность ферментов, функциональную активность иммунной системы, а также способствуют усвоению других микроэлементов, проявляя синергический эффект. Благодаря иммуностимулирующей активности за счет увеличения содержания сиаловых кислот, пропердина, церулоплазмина, гамма-глобулиновой фракции белков, хелаты металлов (меди, кобальта, йода) могут применяться в качестве модуляторов иммунного ответа. Хелатные соединения железа используют для лечения и профилактики железодефицитных анемий не только в ветеринарной, но также и в гуманной медицине. В статье на основе анализа литературы из баз данных Scopus, CyberLeninka, PubMed, РИНЦ и других систематизированы научные знания по проблеме конструирования и синтеза хелатных соединений металлов с использованием органических носителей. Дано научное обоснование использования аминокислот и органических кислот в качестве органических носителей соединений металлов, витаминов и других соединений. Рассмотрен механизм биологического действия хелатных соединений на патогенез микроэлементозов животных, а также описаны преимущества применения хелатных соединений для их терапии и профилактики.

Ключевые слова: обзор, хелатные соединения, органические носители, биологическое действие, железодефицитная анемия, патогенез, профилактика, лечение

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Для корреспонденции: Горковенко Наталья Евгеньевна, д-р биол. наук, доцент, профессор кафедры микробиологии, эпизоотологии и вирусологии ФГБОУ ВО Кубанский ГАУ, ул. им. Калинина, 13, г. Краснодар, 350044, Россия, *e-mail: gorkovenko.n@kubsau.ru*

INTRODUCTION

Prior to the development of chelated drug forms, inorganic mineral compounds were used as supplements in animal husbandry and veterinary practice. Inorganic forms of such metals as copper, iron, zinc, manganese, cobalt, etc. were used for treatment and prevention of poultry and animal diseases for many years. All of them had high toxicity and caused multiple adverse effects [1, 2, 3, 4].

The selection of organic carriers and the study of the toxicological characteristics of new chelated drugs open up new opportunities not only for the development of high and waste-free cultivation technology, but also, very importantly, for obtaining high-quality and safe products [5, 6].

According to numerous scientific papers, amino acids and organic acids have proved to be the best organic carriers. During chelation mineral compounds and vitamins are easily integrated into the organic carrier molecule and are practically freely delivered to the body for metabolic processes [7, 8]. Amino acids used as the organic carrier have a number of advantages over other carriers, in particular those having a sulfate form. Such forms of organic compounds are almost completely involved in the metabolic process and participate in the biochemical reactions of synthesis of new organic substrates and energy in the body of animals and birds. This entails an increase in productivity, preservation, better absorption of feed nutrients and an increase in immune status [9]. These organic complexes have a number of advantages over non-organic forms. One of the advantages is low toxicity for livestock and poultry, as well as decreased dosages with the same biological effect [10, 11]. Besides, the use of chelated drug forms in many aspects solves the environmental problem, which is highly acute for ecologists in regions with developed animal husbandry [12].

A very important point is that the chelate complex is not hydrolyzed by enzymes of the digestive tract until it is absorbed in the small intestine and exposed to substances that can slow down their metabolism. Almost all metals, with the exception of silver (I) and copper (I) compounds, are suitable for the chelation process. Livestock and poultry are most sensitive to mineral compounds such as iron, zinc, copper, cobalt and manganese. These minerals have specific activity [13, 14, 15]. Chelated mineral compounds are better absorbed, have a positive effect on the growth and development of food-producing animals and poultry, which ultimately affects the quality indicators of the products obtained [16, 17, 18].

The purpose of this paper was to generalize and systematize scientific knowledge on the problem of constructing and synthesizing chelated metal compounds using organic carriers based on literature analysis. The Scopus, CyberLeninka, PubMed, RSCI and other databases were used to conduct scientific research.

The most important stage in the development of chelated drug forms is the selection of organic carrier. The amino acid glycine is used as a source of organic carriers. This amino acid is a derivative of acetic acid and a representative of fatty acids. Its biological function is producing a calming effect on the processes of arousal in different parts of the central nervous system. It has a nootropic effect. A dipeptide consisting of two glycine molecules is included in the composition of drugs with hemostatic properties. The amino acid glycine is proteinogenic, optically inactive. It occurs in a free state in animals and plants. This acid is found in the compounds such as glutathione, neuropeptides and antibiotics. This amino acid, which is also part of the bacterial cell wall, was isolated from gelatin in the early 19th century. Glycine is the starting compound for the biosynthesis of interchangeable amino acids, this amino acid is the "supplier" of the amino group in the synthesis of the hemoglobin chromoprotein. Being a part of the polypeptide chain, it participates in the formation of the primary structure of all proteins. It has been proven that glycine participates in the biosynthesis of protoporphyrin – a compound that is a precursor of the pigment chlorophyll and heme. Glycine can be attributed to neurotransmitters, since all the processes that it regulates are reduced to metabolic and receptor actions. The receptors that contain glycine are located in the parts of the spinal cord and brain. Glycine, acting on receptors, reduces the release of glutamic and gamma-aminobutyric acids from them. As a result of the increased release of glutamate, glycine, along with glutamic acid, protects the body from overexcitation processes. Glycine can exhibit an inhibitory effect both with gamma-aminobutyric acid receptors and with its own receptors. Glycine is used as organic carrier in modern pharmacology for development of chelated compounds with alkaline and alkaline earth metals such as lithium, calcium, and magnesium [7, 11].

The research literature contains data on the effect of chelated compounds of amino acids with lithium on growth and development of livestock. As a result of stress, this composition normalizes the work of the hypothalamic-pituitary system, weakening the influence of stress factors on the body. Chelated lithium compounds were subjected to comparative studies. Lithium glycinate and lithium carbonate prevent anemia, have a positive effect on the body growth and development, but lithium glycinate demonstrates a stronger effect in commercial raising of livestock and poultry under stressful situations [8, 19].

Amino acid compounds with magnesium and calcium salts exhibit a high biological effect, and are available as independent medicinal products in the pharmacological industry. Magnesium glycinate promotes better adsorption of magnesium in the intestine, making it more accessible for participation in biological oxidation processes in order to generate energy with adenosine triphosphate, strengthen bone tissue, and relieve tension in muscle tone [8, 9].

L-hydroxyproline was isolated at the beginning of the last century. Currently, this compound is derived from collagen and other proteins as a result of hydrolysis. During the hydroxylation of proline, the interchangeable amino acid oxyproline is synthesized, being involved in the metabolic process, two very important biologically active compounds are formed from it: pyrrole-2-carboxylic and glutamic acids [20]. The amino acid hydroxyproline, in addition to participating in the formation of proteins, is involved in the synthesis of elastin and collagen. The composition of the collagen molecule includes the amino acids hydroxyproline, glycine, and proline. The collagen protein molecule itself has the shape of a three-dimensional spiral. Drugs with anti-inflammatory and antipyretic effects have been developed on the basis of L-proline, 4-hydroxyproline compounds, as well as salts thereof; 4-hydroxyproline is used as the main substrate in the synthesis of drugs with antifungal action. At the cellular level, this compound restores damaged cellular structures by affecting the collagen synthesis, which has found its application in cosmetology. Chelated compounds of 4-hydroxyproline with various salts of lithium, calcium, and magnesium are described in the literature, but their physico-chemical properties and synthesis are not presented. The production of 4-hydroxyproline salts with elements such as lithium, sodium, and magnesium is based on neutralization reaction [2, 21].

Chelated compounds have a wide range of biological effects, ranging from increasing the activity of many important enzymes, as well as ensuring the processes of body protection from adverse external factors [22]. Some compounds, such as copper and zinc, improve the absorption of cobalt, providing the so-called synergistic effect. Excessive protein and iron content slow down the process of its absorption in the gastrointestinal tract [23].

Numerous scientific studies have addressed the role of mineral compounds in humans and animals, daily norms as well as the main sources of intake have been determined. Biogeochemical provinces with a certain content of macro- and microelements in soil and plants, as well as their effect on the physiological state of animals contained in these zones, have been established [24, 25, 26]. Since the middle of the last century, scientists of the Kazan State Academy of Veterinary Medicine named after N. E. Bauman have been conducting scientific work on the study of chelated forms of mineral compounds [5, 8, 11]. The main metal complexes were synthesized on the basis of copper and organic compounds such as lactocasein and lactoalbumin, and copper chelates with destructive proteins were obtained, which were isolated from animal tissues and organs [11, 27, 28].

The positive effect of organometallic compounds on the synthesis of keratin protein and serum proteins has been proven. Metallochelates have a pronounced effect on the production of antibodies in various types of vaccination. Injectable forms of chelates of copper, cobalt, iodine are able to stimulate the protective functions of the body by increasing the content of sialic acids, properdin, cerruloplasmin, gamma globulin fraction of proteins. These data have been confirmed in both laboratory animals and experimental livestock populations [2].

Iron deficiency is the most studied form of micronutrient deficiency. Iron deficiency anemia in animals occurs due to lack of iron being a constituent of the chromoprotein hemoglobin, which provides oxygen transportation [29]. Iron is necessary for the implementation of all vital functions of the body, ensuring its growth, and, accordingly, the volume of circulating blood. Piglets have intensive metabolic processes, so they are sensitive to iron deficiency. Piglets receive iron with maternal milk on the first day of life, with feed, as well as endogenously during the breakdown of red blood cells. The composition of sow milk contains enough biologically active compounds involved in the synthesis of new compounds, adenosine triphosphate, but little iron. Due to the breakdown of red blood cells, maximum one percent of iron enters the bloodstream daily. It is absorbed from the plasma by cells of the reticular-endothelial system [30, 31]. This system does not function well in young animals, the process of iron deposition is disrupted, therefore, its deficiency occurs in the body. The disease is aggravated by the fact that piglets are born with low iron reserves of no more than 50 mg. In this regard, if there is no external supply of this trace element, the iron deficiency is detected within a week after birth, and anemia is recorded a month later [32]. The severity of the disease is aggravated by the lack of intake of mineral compounds and vitamins into the body.

Considering the pathogenesis of iron deficiency anemia, it is possible to state a decrease in the amount of hemoglobin, as well as a decrease in the activity of iron-containing enzymes, especially cytochromes involved in the biological oxidation chain. Iron, which is part of hemoglobin, forms a complex consisting of iron and oxygen, which is actively involved in metabolic processes. With its deficiency, the phenomenon of hypoxia is observed, which negatively affects the work of all organs.

Compensatory mechanisms develop in conditions of hypoxia, that can lead to organ hypertrophy [33]. In the first days of life, iron deficiency is observed in young animals of almost all animal species, but in calves, foals and lambs this condition is temporary and does not turn into a chronic form. Piglets are more susceptible to this pathology, the most intense clinical symptoms appear one and a half months after birth. The degree of pathological changes occurring in the body will largely depend on the etiological factor, local organotropic effects, the degree of toxic effects on the body, as well as the body's resistance [34].

The manifestation of this disease is characterized by a lag in growth, a decrease in the natural resistance of young farm animals, in particular, piglets are sensitive to iron deficiency. The clinical symptom of iron deficiency anemia is the pale coloration of the visible mucous membranes which subsequently turn yellow. The animals are lethargic, stunted in their growth, the bristles stick up, the skin looks wrinkled. Appetite is either absent or perverted. Digestive disorders are also noted, constipation alternates with diarrhea. Blood tests show a decrease in hemoglobin levels from 10 to 3.5 g/%. The content of erythrocytes remains normal, but their qualitative composition changes, erythroblasts are detected in blood [32, 35].

To make a diagnosis, the amount of iron and hemoglobin in blood and parenchymal organs is determined. A specific marker of anemia is the color index of blood. At the same time, the feeding diet is analysed. Anemia occurring in the setting of infectious and invasive diseases is excluded by means of differential diagnosis [35].

Pharmacotherapeutic intervention in iron deficiency anemia should be aimed at normalizing all links of the pathological process and eliminating all symptoms of the disease [36]. Iron dextran drug products containing carbohydrate-binding colloid iron (III) are of great scientific importance in the treatment and prevention of iron deficiency anemia. These medicinal products are produced in almost all countries of the world. The main difference between all manufactured preparations is that the carbohydrates included therein form different chemical compounds, and the iron content ranges from 50 to 200 mg/mL [37, 38]. The advantage of iron dextrans over drug products containing iron salts is that even one 3 mL dose injected to the animal has a therapeutic effect and prevents the development of iron deficiency anemia. With a significant increase of the dose, the amount of iron in blood may increase leading to the development of hemosiderosis [39, 40].

The opinions of scientists regarding dosages for parenteral administration vary. There are developments on combined antianemic drugs. They include copper chloride, sodium and cobalt salts, and vitamins B which are of great importance. The drugs may also contain raw materials of plant and animal origin, amino acids and biologically active compounds. The compatibility of mineral and vitamin supplements in premixes and compound feeds ensures their bioavailability [41, 42].

CONCLUSION

To date, a fairly large number of study results have been obtained on the development of chelated metal compounds and the rationale of their use for the treatment and prevention of various pathologies of livestock and humans. Currently, amino acids such as glycine, hydroxyproline and others are mainly used for the synthesis of chelated compounds as organic carriers for alkaline and alkaline earth metals (lithium, calcium, magnesium). The effective action of chelated metal compounds is based on metabolic and receptor reactions. The action of chelates depends on a number of factors. Firstly, it depends on which metal ion is included in the composition of the compound, and secondly, on the organic carrier used. Different variants of chelate compositions are used both for the prevention and therapy of pathologies associated with iron, cobalt and other macro- and microelement deficiencies in livestock and poultry: for instance, in case of iron deficiency anemia, lack of cobalt. One of the advantages of chelated compounds is their high bioavailability due to the presence of organic carrier. This predetermined their use as preventive and therapeutic drugs that significantly surpass their non-organic counterparts. In addition, the advantage of chelates is the absence of an accumulation effect in animal tissues and organs, which makes it possible to obtain safe livestock products of high quality. Thus, the development and reasonable administration of new chelated compounds is promising as they can be used to solve a wide range of problems in veterinary medicine.

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INFORMATION ABOUT THE AUTHORS / ИНФОРМАЦИЯ ОБ АВТОРАХ

Andrey G. Koshchaev, Academician of the RAS, Professor, Dr. Sci. (Biology), Professor of the Department of Biotechnology, Biochemistry and Biophysics, Kuban State Agrarian University named after I. T. Trubilin, Krasnodar, Russia;
https://orcid.org/0000-0002-3904-2860,
e-mail: koshhaev.a@kubsau.ru

Natalya E. Gorkovenko, Dr. Sci. (Biology), Associate Professor, Professor of the Department of Microbiology, Epizootology and Virology, Kuban State Agrarian University named after I. T. Trubilin, Krasnodar, Russia; *https://orcid.org/0000-0002-5112-2679,*
e-mail: gorkovenko.n@kubsau.ru

Anastasia V. Kosykh, Postgraduate Student, Kuban State Agrarian University named after I. T. Trubilin, Krasnodar, Russia;
https://orcid.org/0009-0006-0561-6420,
e-mail: nastyantipova170196@icloud.com

Кощаев Андрей Георгиевич, академик РАН, профессор, д-р биол. наук, профессор кафедры биотехнологии, биохимии и биофизики, ФГБОУ ВО Кубанский ГАУ, г. Краснодар, Россия;
https://orcid.org/0000-0002-3904-2860,
e-mail: koshhaev.a@kubsau.ru

Горковенко Наталья Евгеньевна, д-р биол. наук, доцент, профессор кафедры микробиологии, эпизоотологии и вирусологии ФГБОУ ВО Кубанский ГАУ, г. Краснодар, Россия;
https://orcid.org/0000-0002-5112-2679,
e-mail: gorkovenko.n@kubsau.ru

Косых Анастасия Валерьевна, аспирант ФГБОУ ВО Кубанский ГАУ, г. Краснодар, Россия;
https://orcid.org/0009-0006-0561-6420,
e-mail: nastyantipova170196@icloud.com

Darya V. Antipova, Cand. Sci. (Biology), Laboratory Researcher, Laboratory for Development and Quality Assessment of Feed and Feed Additives of Kuban State Agrarian University named after I. T. Trubilin, Krasnodar, Russia;
https://orcid.org/0000-0002-2662-5434, e-mail: rauzhena93@mail.ru

Антипова Дарья Валерьевна, канд. биол. наук, лаборант-исследователь лаборатории разработки и оценки качества кормов и кормовых добавок ФГБОУ ВО Кубанский ГАУ, г. Краснодар, Россия; *https://orcid.org/0000-0002-2662-5434, e-mail: rauzhena93@mail.ru*

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Вклад авторов: Кощаев А. Г. – научное консультирование, концепция представления материалов; Горковенко Н. Е. – подбор и анализ научной литературы по заявленной проблеме, интерпретация данных, подготовка и редактирование текста; Косых А. В. – подбор и анализ научной литературы, подготовка текста; Антипова Д. В. – подбор и анализ научной литературы по заявленной проблеме, интерпретация данных, подготовка текста.