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REVIEW PAPER

COPPER – AN ESSENTIAL MICRONUTRIENT FOR CALVES AND ADULT CATTLE

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Abstract

Trace elements, including copper, are crucial for the proper course of various biochemical processes occurring in the organisms of young and adult ruminants. Copper plays a key role in cell development and metabolism, since it exhibits strong antioxidant activity. Being a constituent of various metalloenzymes and metalloproteins such as: cytochrome C oxidase (Cox), superoxide dismutase (SOD) and ceruloplasmin (Cp), copper participates in the regulation of processes of cellular respiration, carbohydrate and lipid metabolism and collagen formation. The deficiency of this element has a significant impact on the development, growth and reproduction of farm animals, including cattle. Although this element is an essential micronutrient for ruminants, its over-supply in the body can cause severe symptoms of poisoning. In the time when emphasis is placed on animal welfare as well as intensive livestock production, it is necessary to be aware of the role that copper plays in bovine organism. Appropriate dosage of this microelement in feed additives used in cattle nutrition is required in order to avoid negative effects of either deficiency or excessive mineral supplementation, as both nutritional deficiencies and intoxications are responsible for significant economic losses in livestock production and inferior welfare. The aim of this article is to review information on the effects of copper on the functioning of adult cattle and calves, and on the effects of deficiency and toxicity of this element.

Keywords: bovine, cattle, copper, trace elements.

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INTRODUCTION

Trace elements, including copper (Cu), zinc (Zn), manganium (Mn) and selenium (Se), accompanied by macroelements are crucial for the proper functioning of calves and adult cattle (Żarczyńska et al. 2012). They are essential to maintain health and physiological functioning of the immune system (Terpiłowska, Siwicki 2011). Microelements are also constituents of various enzymes and proteins, which support a number of metabolic processes, including ones involved in the growth and productivity of farm animals. Interactions between nutrition, immune processes and disease resistance are very complex. Any micronutrient deficiency during the intrauterine fetal development or in early growth may have adverse effects on animals' health in the future (Enjalbert 2009).

Copper has been identified as a necessary microelement for ruminants already in the 1920s and 1930s, by laboratory and field observations in cattle and sheep. It is involved in the fundamental processes responsible for cell metabolism, development and integrity. Diseases associated with copper deficiency and toxicity in animals are a frequent subject of scientific research, but livestock such as cattle is relatively rarely used as a model for research concerning trace elements metabolism and interactions (Humann-Ziehank 2016).

The aim of this article is to review information on the influence of copper on the functioning of adult cattle and calves and on the effects of Cu deficiency and toxicity.

THE IMPORTANCE OF COPPER IN AN ANIMAL ORGANISM

Copper is a component of number of metalloenzymes and copper-containing metalloproteins, which are recognized in the higher organisms as essential for the proper development and functioning of the skeleton as well as the cardiovascular, nervous and reproductive systems (Cousins 1985, Sharma et al. 2008). It plays a key regulatory role in many biochemical processes, including cellular respiration, carbohydrates, lipid, collagen, elastin, melanin and catecholamine metabolism (Tomlinson et al. 2004, Andrieu 2008). However, the most important ones are oxidation and reduction processes, where copper, being part of cytochrome C oxidase (Cox) and superoxide dismutase (SOD), exerts an influence on the oxidative balance, demonstrating its antioxidant activity. According to Arthington et al. (1996) superoxide dismutase, which catalyzes the transformation of O^{2-} into H_2O_2, due to its oxidative action can play a significant role in the process of phagocytosis and protection against the consequences of oxidative stress. Copper is essential in maintain-

ing a healthy appearance of hair, because it is a part of monoamine oxidase (MAO) involved in collagen maturation and tyrosinase, which catalyzes synthesis of melanin responsible for hair colour. Cu is also involved in the absorption and metabolism of iron in the body in the form of ceruloplasmin (Cp) (Hostetler et al. 2003). This protein oxidizes ferrous ion (Fe^{2+}) to ferric ion (Fe^{3+}) and facilites the incorporation of iron into ferritin, thereby inhibiting the iron uptake by microorganisms (Saenko et al. 1994). It is also an acute phase protein, whose concentration in the organism increases during illness and may be important in the removal of peroxide radicals (Broadley, Hoover 1989). This element is essential for the proper functioning of human and animals organisms as well as for pathogens attacking them. It is noteworthy that due to its oxidative properties and the ability to interfere with the active center of Fe-S metalloprotein, it may exhibit toxic properties. The view that farm animals use this mechanism in the field of defense against microbes has been relatively recent (Besold et al. 2016). In the study of Ward et al. (1997), copper deficiency alone and coupled with high dietary Mo or Fe produced inconsistent immune function responses, indicating that Cu deficiency may not affect a specific immune function of calves.

Copper, along with vitamin E and A, and Zn and Se, plays a key role in keeping a healthy udder, especially under stress conditions (Sordillo et al. 1997, Machado et al. 2013). Scaletti et al. (2003) found that the severity of mastitis caused by *E. coli* infection decreased after administration of copper, but the treatment did not affect the duration of infection. In addition, an appropriate level of copper in animal feed is necessary to optimize the functioning of the whole immune system, as copper reduces the risk of metabolic and oxidative stress in dairy cows (Cortinhas et al. 2010).

COPPER STATUS IN RUMINANTS

In cattle, the bioavailability of nutrients, including micronutrients, is dependent on a number of factors, like general health, nutrition and state of the digestive tract (because its dysfunction can inhibit the absorption of copper from the feed) (Radwińska, Żarczyńska 2014), exposition to stress (because the excretion of copper in the urine increases significantly under the influence of stress) (Fairweather-Tait, Hurrell 1996) and the nature of the element itself and its specificity. Copper is considered to be a relatively absorbable element (Żarczyńska et al. 2017). Its absorption in ruminants occurs partly in the forestomach, where the involvement of microflora occurs, and partly in the small intestine, where copper ions are bound by metallothionein-low molecular weight protein (Gooneratne et al. 1989). Albumins are responsible for the transport of copper to the liver, which is the main organ that stores this element in mammals (Gordon et al. 1987). The relationship between the concentration of copper in blood and liver is variable

(Muryan, Mason 1992). Therefore, the determination of copper levels in serum appears to be an inadequate indicator to illustrate the supply of copper in the body. Laven et al. (2007) believe that determination of the Cu:Cp ratio in the blood serum could be a good reflection of the copper content in the cow's organism and its metabolism. In turn, according to Engle et al. (2001), copper deficiency causes reduction of cholesterol in the blood plasma. Consequently, it was concluded that this parameter might be utilized to reflect the status of the body's copper supply. However, in spite of attempts to find one specific parameter that evaluates the copper status in an organism, determination of the Cu content in the liver remains the most reliable and indispensable indicator of the Cu status in ruminants (Hepburn 2009, Balemi et al. 2010).

COPPER DEFICIENCY AND SUPPLEMENTATION IN CATTLE

Diseases resulting from copper deficiency and poisoning are common and relatively well described in veterinary medicine. Copper-deficient states may be primary and secondary, and can be accompanied by deficiencies of other elements, as in the case of the „coast disease" or „salt sickness", which are accompanied by cobalt (Co) deficiency and can affect adult cattle as well as calves. Cu deficiency in ruminants is generally secondary, and develops due to decreased absorption of copper, in the presence of antagonists of this element in feed, such as molybdenum (Mo), sulfur (S) and iron (Fe) (Suttle 1991). In areas where feed is poor in copper antagonists, these deficiences are mainly of primary character and occur because of an insufficient copper content in feed. López-Alonso et al. (2002) observed that the copper concentration in the liver is closely correlated with its content in the soil. Floodplains and areas with high levels of surface water, washed-out soluble sands and alkaline clays belong to the soils that are poor in copper and conducive to the occurrence of its deficiences. Peat and marshes, despite containing relatively large amounts of copper in their composition, have this element incorporated in complexes that are inaccessible to herbivores.

A proper supply of copper to ruminants organism is crucial for the correct course of important, enzymatically controlled processes. There are a number of syndromes related to copper deficiency, depending on the place of occurrence, e.g. the „falling disease" in Australia and New Zealand, „reclaim disease" and „peat scours" in Ireland and Canada, and in Scotland „pine" in calves.

In addition to the diseases known under local names**,** copper deficiency is manifested by a number of more or less specific symptoms. Cattle suffering from insufficient copper supply exhibit a reduced appetite, are apathetic and weakened and persistent longlasting deficiency will lead to cachexia. Dairy

cows during lactation show reduced milk yield and fat content in milk The most characteristic are changes in the coat, which include: fading of the coat's colour and loss of hair around the eyes (so called spectacled appearance), neck, thorax and forelimbs. Moreover, copper deficiency can cause the pallor of mucous membranes due to the malfunction of iron incorporation into haemoglobin and development of anaemia, abnormal bone growth and spontaneous fractures caused by the weakened osteoblast function, ataxia, spinal cord hypomyelination, fragility of the capillaries, degeneration of the myocardium, reproductive disorders and reduced resistance to infectious diseases.

Enjalbert et al. (2006) suggest that an insufficient copper status will not contribute significantly to disturbances in organisms of adult animals, while it would be an important factor conducive to the risk to the health and growth of young animals. The micronutrients are transferred to a large degree through the placenta to the fetus, and in a later stage through colostrum and milk to the calf (Banafsheh et al. 2012). In calves, the effects of deficiencies can therefore be observed in newborn animals, because the reservoir of trace elements in their body will be correlated with the mother's nutrition. In order to prevent this, it is necessary to supplement the minerals in injections at an early age. According to Teixeira et al. (2014), calves that received the addition of micronutrients had improved the neutrophil function, had a greater phagocytic capacity and higher activity of glutathione peroxidase, in addition to which these animals had less frequent events of diarrhoea. The susceptibility of ruminants to the state of copper deficiency decreases with age, also due to the fact that this element plays a significant role in the rapidly growing calf organism. An inadequate Cu status of a calf will result in several abnormalities of the locomotor system, including lameness, stiffness of movement, thickening of the growth cartilage of metacarpal and metatarsal bones, bone fractures, temporary hind leg ataxia, dog-sitting posture and such general symptoms as apathy, reduced appetite and diarrhoea.

Diagnosis of copper deficiency in individual animals and herds should be based on clinical signs and estimation of copper levels in the blood serum and liver. Forage analysis for copper, molybdenum, iron and sulfate followed by water analysis for sulfate help to diagnose and plan further treatment.

Recommended daily dietary copper intake for cattle oscillates from 8 to 20 mg kg^{-1} of dry matter and depends on several factors (Mullis et al. 2003, Sathler et al. 2017). Body weight, growth rate, type of production (beef or dairy), milk yield, late pregnancy and presence of copper antagonists in feed are major aspects that influence daily copper requirements. Pregnant cows as well as young, growing animals require higher levels of copper in a daily feed ration in comparison with mature cattle at maintenance (Costa e Silva et al. 2015). Traditionally, copper supplements have been fed as inorganic salt cupric sulfate, but nowadays a lot of minerals, including copper are supplemented orally using an organic form, in which the mineral is bound to an

organic (i.e. carbon-containing) molecule, typically an amino acid or protein. Copper can be supplemented to cattle through various ways, including licks, water and feed supplements, oral pellets or boluses and injections. Before choosing a specific form of supplementation, it is worth taking into account that copper intake can vary between individuals in a herd when feed and water supplements are considered. Oral pellets or boluses are very safe because of their slow release formulation, but might not be enough to correct severe cases of deficiency, which might require an individual approach with incjectable formulas. After taking into consideration advantages and disadvantages of different forms of copper supplements, it can be seen that Cu supplementation might be a challenge for veterinary practitioners and farmers.

COPPER ACCUMULATION AND TOXICITY

An adequate macro- and microelements status in an animal organism is vital to ensure a succesful transition period from late gestatiom into early lactation (Andrieu 2008). However, high productivity and milk yield of dairy cattle make it difficult to establish the proper balance of feed rations. Feed supplementation with microelements is an indispensable element of dairy cattle rearing as well as dairy industry. Therefore, the risk of an excessive copper intake increases. Such a situation could lead to copper accumulation in the liver and consequently contribute to the development of chronic copper intoxication.

Kendall et al. (2015) define copper overloading as an excessive accumulation of this element in the liver, considered to be one of the reasons for developing the state of chronic copper toxicity, which in recent years has become a more frequent problem, especially in dairy cattle herds, in many countries around the world. The aforementioned authors also give several reasons for the presence of this tendency. Among them, the most important seems to be the fact that even with extensive knowledge about copper, its interactions with various factors, despite conducting many studies, are not fully understood and even misinterpreted. One cannot ignore the attitude of many farmers who, seeing certain results of copper supplementation, expect them to improve after increasing the dose. Such actions may contribute to the imbalances between the feed rations and excessive copper feeding coming from various sources. As a consequence**,** animals may be exposed to increased accumulation of this element in the liver. Miranda et al. (2009) stated that soils with a relatively low calcium to magnesium ratio and high concentrations of nickel, iron, cobalt and chromium (so called serpentine soils) have a significant impact on the accumulation of Ni and Cu in cattle, since tissue accumulation in animals is associated with metal concentrations in soils and fodder. Under such conditions, a relatively high percentage of animals exhibit Ni and Cu concentrations in tissues indicating the risk of toxicity.

Copper toxicity and poisoning have been defined by Bidewell et al. (2012) as an increased copper intake (greater than 40 mg Cu kg^{-1} of dry matter intake) resulting in necrotic liver disease causing haemolytic crisis and post mortem manifested by the enlarged liver with an orange tint, haemolytic anaemia, jaundice, haemoglobinuria, methemoglobic colour of blood and tissues, and dark swallen kidneys. Intoxication with Cu may be acute or chronic depending on its origin. Contrary to chronic copper poisoning, which is caused by prolonged ingestion of high doses of this element, acute poisoning may occur as a result of a single administration of a very high dose of Cu or its increased release from the liver due to a damage of this organ or stress factors such as transport, feed changes, fasting and advanced pregnancy (Grace et al. 2010, Johnson et al. 2014). Excessive copper ingestion leads to excessive but asymptomatic accumulation of this micronutrient in the liver, which is due to the fact that ruminants have a relatively high potential for copper accumulation in this organ (López- Alonso et al. 2000). Symptoms of the disease begin to appear only when the capacity for storing Cu by the liver cells is exceeded and releasing significant amounts of this element into the blood stream occurs. Elevated levels of Cu in the bloodstream within a day will result in massive degradation of erythrocytes, which leads to haemoglobinemia, haemoglobinuria, and consequently inhibits cellular respiration and causes death. The clinical picture of acute copper poisoning includes rapid decrease in appetite, increased thirst, apathy, general weakness, lack of forestomachs' motility and yellowish colour of mucous membranes. In cases of chronic toxicity, the symptoms are less severe and less characteristic, including reduced milk yield, hair loss, fertility disorders and high calves' mortality. Morgan et al. (2014), recommended immediate removal of all Cu-containing supplements and administration of 200 mg of molybdenum to the cows fed once a day for a period of approximately 4 weeks. After treatment, if such a herd requires further copper supplementation, the program of its administration to animals should be correlated with the monitoring of the copper concentration in the liver.

CONCLUSIONS

Due to the functions that copper plays in living organisms, its deficiencies may entail the risk of health and reproduction disorders in beef and dairy cattle herds, thus contributing to the reduced productivity of the farms. Although it is essential for the proper functioning of organisms, its toxic properties should not be forgotten. Therefore, in the era of intensive livestock production, it is essential to select the appropriate dosage of this microelement in feed additives used in ruminant nutrition in order to avoid the negative effects of both deficiency and excessive mineral supplementation. It is very important to have an individual approach to ensure adequate sup-

ply of micronutrients in each herd, as nutritional deficiencies and intoxications contribute to significant economic losses in livestock production. At this time, it is important to pay special attention to ensure that the animals have adequate levels of micronutrients in their daily feed ration.

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