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Importance of dietary copper supplementation in ruminant production: A review

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Abstract

Incessant copper deficiency in ruminants should not be underestimated because copper is known as an essential trace element with the ability to perform multiple functions in the intracellular system of animals such as enzyme-coenzyme catalytic reaction; thus it is associated with the function of a number of enzymes in the system such as oxygenase including cytochrome-c-oxidase, copper-zinc superoxide dismutase, lysyl oxidase. It is required for cellular respiration, free radical defense, haemoglobin synthesis, antibody development, and antioxidant production, all of which contribute to proper immune function in animals and aid in the maintenance of optimal production and reproduction.In conclusion, ruminants are more vulnerable to copper deficiency than any other living organism due to the complex nutritional interaction occurring in the rumen, dietary copper must always be supplemented in their diet.

Keywords: Hypocuprosis, thiomolybdate, immunity, metalloenzymes, dismutation, antioxidant

Importance de la supplémentation en cuivre alimentaire dans la production de ruminants: une critique

Résumé

Un déficit incessant de cuivre dans les ruminants ne doit pas être sous-estimé car le cuivre est connu comme un élément de trace essentiel avec la possibilité d'effectuer plusieurs fonctions dans le système intracellulaire d'animaux tels que la réaction catalytique enzymatique-coenzyme; Ainsi, il est associé à la fonction d'un certain nombre d'enzymes dans le système telles que l'oxygénase, y compris de cytochrome-oxidase, de superoxyde de cuivre-zinc démutase, de la lysyle oxydase, il est nécessaire pour la respiration cellulaire, la défense radicale libre, la synthèse de l'hémoglobine, le développement d'anticorps et la production antioxydante, qui contribuent toutes à une fonction immunitaire appropriée chez les animaux et à l'aide au maintien de la production et de la reproduction optimales. En conclusion, les ruminants sont plus vulnérables à la carence en cuivre que tout autre organisme vivant en raison de l'interaction nutritionnelle complexe dans la Rumen, le cuivre alimentaire doit toujours être complété dans leur régime alimentaire.

Mots-clés: hypocurogose, thiomolybdate, immunité, métalloenzyzymes, démocalisation, antioxydant

Introduction

Minerals can simply be classified as macro or micro elements having significant contribution in a variety of biological functions. The study of minerals is cumbersome simply because minerals interact with each other as well other nutrients. Based on this singular fact, it is so germane to understand the nutritional interactions occurring in the rumen in order to solve problems associated with animal's nutrition. Copper (Cu)are micronutrients required in very minute amounts having important roles in the body metabolic activities, growth, production and reproduction. Ruminants often develop signs of copper deficiency simply known as hypocuprosis in cases where the Cu level >10ppm. This occurs when copper antagonists are high in ingested diet. Minerals that antagonize Cu include molybdenum (Mo), sulphur (S) and iron (Fe) (Suttle, 2010). Primary Cu deficiency is simply described as the inadequate intake of copper while secondary Cu deficiency is when the less supply of copper in pastures is due to dietary interfering factors. When the ratio of Cu to Mo ranges from 5 to 1 or10 to 1, cattle perform wonderfully. In addition, secondary Cu deficiency is as a result of the excess amount of molybdenum coupled with sulphur (S), thus, forming thiomolybdate complexes; poorly absorbed from the lower gastro intestinal tract(Ahmad *et al.,*2009). Molybdenosis is simply referred to high molybdenum levels in the blood causing looseness of bowels in cows. Higher level of Mo content had been reported by Mills *et al.* (1976) to cause Cu insufficiency in ruminants. Although cupric sulfate had been referred to as the standard source of copper supplementation, in which other copper sources are compared to (Spears, 2003). In an experiment conducted by Ward *et al.*(1996), copper proteinate was more bioavailable than cupric sulfate in cattle fed diets containing high level of molybdenum but not in others (Wittenberg *et al.,* 1990). Animals fed forage-based diets are often exposed to high levels of iron (Fe)content but the role of Fe on Cu absorption had been reported by Humphries *et al.* (1983)to be partially dependent on S availability. However, the formation of FeS in the rumen content had been ascribed by Suttle (2010) to be a critical step for Fe to antagonize Cu absorption. It was further demonstrated by Arredondo *et al.* (2003) that the presence of excess Fe can compete with Cu for its absorption at the intestinal level. High intake of Fe concentration in ruminant are majorly through their drinking water, soil or forage ingested. Iron had been reported by Lee and Grace (1997) as an antagonist enhancing the decline of Cu status in both cow and sheep. It was reported that monogastric animals are capable of absorbing 30-75%, adult ruminants absorbed 1-10% but before the functional rumen fully developed, it's absorption can be as high as 70-85% of the dietary copper supplied (Underwood and Suttle, 1999; 2001; Linder, 2002). Complex interactions occurring in the rumen compartment had been attributed as the major cause of low absorption of copper in adult ruminants (Spears, 2003), thus includes Cu-S-Mo (Suttle, 2010), and Cu-S (Arthington and Pate, 2002) antagonisms. However, the amount of Cu absorbable in a feed or supplement will definitely depend on interactions with other ration constituents, particularly those high in S, Mo and Fe. Dietary copper needed to supply Cu requirements for maintenance, growth and lactation varies with the age of the animal, the chemical form of dietary Cu and the presence of dietary substances interfering with Cu absorption. Copper availability differ widely with feed sources and the reasons not completely understood such that fresh grass is a poor copper source while certain cereal by-products are good sources of copper for sheep. Sheep are more prone to scouring or diarrhea than any other ruminants as the excreta are mostly liquid (Underwood and Suttle, 2000). Dairy cows with severe diarrhea case will react to copper treatment within 12 hours (McDowell, 2003). It is reported that supplementation of Cu in a bioavailability form (organic complexes) could overcome the adverse effects of antagonists like Mo and S. Although, copper supplementation has generally been accepted and required to overcome adverse effects caused by deficiency of these elements. More so, addition of Cu in a readily available form that is not markedly influenced by Cu antagonists would be a logical means to overcome these problems (Du *et al.,* 1996). Improved availability of copper in the form of organic complexes had been suggested over the commonly inorganic Cu sources (Apgar and Kornegay, 1996). However, the use of organic form of Cu can improve the level of Cu in the body and hence improve the results obtained from Cu supplementation than that obtained in inorganic form, with respect to lipid metabolism and the reduction of cholesterol in meat. Copper (Cu) is an essential element required by animals for numerous biochemical functions such as enzyme-coenzyme catalytic reaction, thus, it is associated with the function of a number of enzymes. It is an important constituent of the growing number of cuproenzymes and copper metalloprotein with functions as diverse as electron transfer (Cobine *et al.,* 2006), pigmentation (Sendovski *et al.,* 2011; Xu *et al.,* 2013) and oxidation resistance (Wang *et al.*,2013).

Table 1: Effect of copper on some enzymes

Enzymes	Biological Functions	Clinical Significance
Cerruloplasmin	Fe^{2+}, Fe^{3+}, copper and iron transport	Anaemia
Copper-zinc Superoxide dismutase (SOD)	Dismutation of O_2^- to H_2O_2	Antioxidation
Cytochrome c-oxidase	Terminal electron transfer and function of central nervous system	Anorexia
Tyrosines	Tyrosinase to Melanin	Behaviour

Adopted from Underwood and Suttle (2000)

Influence of Copper supplementation on growth performances

The growth promoting effect of Cu is well established and is amply reviewed by different researchers (Wittenberg *et al.*, 1990; McDowell, 1992; Aina *et al.,* 2010). Mineral supplementation is essential to the livestock in order to overcome the detrimental influences it has on animal performance. Several reports had revealed that minerals supplementation improved animals' performance (Lall *et al.,* 2000). In a previous study conducted by Ward *et al.* (1993) on steers, the growth rate of animals fed $CuSO_4$ supplemented diet was higher when compared with those fed Cu-lysine supplementations within the first 21 days while no disparity were recorded after 98 days. More so, other parameters such as feed efficiency, feed intake, humoral, cellular immune response and ceruloplasmin activity, were not influenced by Cu source (Ward *et al.,* 1993). Higher weight gain was reported for steers on Cu proteinate supplementation (Wittenberg *et al.*, 1990). Datta *et al.* (2007) reported an increased higher body weight gain for goat kids fed organic Cu supplemented diet when compared with those fed inorganic Cu supplementation. Aina *et al.* (2010) reported an increase in weight gain for West African dwarf sheep fed different copper ($CuSO_4$ and $CuNO_3$) supplemented diet. Thus, agreed with Asare-Bediako and Aina (2013) who reported that Cu supplemental diets improved growth performance of sheep in such a way that dry matter intake (DMI), feed conversion ratio (FCR) and average daily weight gain (ADG) were significantly higher in the Cu treated group when compared with those in control. This was attributed to the fact that Cu supplemental diets might have provided the ideal rumen Cu concentration essential to enhance rumination. However, the faster growth rate recorded in Cu supplemented groups might be due to improved feed utilization rather than feed consumption. Feed consumption among Cu-treated group seemed to show similar even though, growth performance differed. Significantly improved DMI and feed conversion ratio (FCR), eventually improved average daily weight gain (ADG) of goats offered Cu salts-based diets. More so, finishing cattle fed Cu supplementation had increased performance (Engle and Spear, 1999; 2000a; 2000b). Furthermore, Zhang *ET AL.* (2007) reported an increase in average daily weight gain and feed efficiency of cashmere goats fed a basal diet containing 7.38mg Cu/kg DM supplemented with 10mg Cu/Kg DM. Although the observation of Cheng *et al.* (2008) contradicted the observation of previous researchers who reported Cu supplementation at 10 or 20 mg/kg DM had no effect on the weight gain and feed efficiency of lambs. Luginbuhl *et al.* (2000) also reported that 10 or 30 mg Cu kg DM over 88 days had no effect on average daily feed intake and daily weight gain of weaned goat kids. Contradicting performance results exist in ruminant fed Cu supplemented diets and the reasons for this variation were ambiguous because several factors could potentially influence an animal's response to Cu supplementation; forms of Cu supplementation (either organic or inorganic), the absence and presence of dietary Cu antagonists (S, Mo, Zn, Fe), initial Cu status of the animal, environmental and health factors, Cu supplemental level and the experimental diets (Arthington and Pate, 2002) and lastly the breed differences in Cu metabolism (Mullis *ET AL.*, 2003). In the presence of adequate amount of elemental Zn in the system, excessive Cu might not influence daily weight gain in the prehaemolytic period (Zervas *et al.,* 1990). In addition to the essential roles played by Cu in metabolic processes, thus it can also produce pharmacological responses under certain conditions which may improve animal's performance. The performance response to Cu in this present study, as reported by Solaiman *ET AL.* (2006; 2007), may have been pharmacological rather than physiological.

Influence of Copper supplementation on blood profile

Copper(Cu)has been described as an antioxidant nutrient for cardiovascular health (Allen and Klevay, 1994). Several studies had suggested that copper supplementation can affect lipid metabolism in ruminants (Engle and Spears, 2000a; Engle *et al.,* 2000a,b,c; Engle and Spears, 2001; Netto*et al.*, 2014). Cu is essential element used in lysyl oxidase, purposely for the integrity of blood vessels, heart, as well as its role in antioxidant enzymes such as ceruloplasmin and Cu-Zn superoxide dismutase. Supplementation of Cu helped to reduce the level of cholesterol in the blood and this was attributed to the inverse relationship between copper and cholesterol, as reported by Soyinka *et al.* (2007). Hypocuprosis simply referred to Cu deficiency in ruminants, thus plays a big role in the development of cardiovascular disease (Al-Bayati *et al.,* 2015). Copper deficiency has been investigated by using ceruloplasmin diagnostically in domestic animals (El-khaiat *et al.,* 2012). Cu supplementation has been described by Solaiman *et al.* (2004) as an essential tool enhancing proper immune function in animals. Cu is essential for proper development of antibodies such as white blood cells and production of antioxidant enzymes(Sharma *et al.,* 2005). Copper performs bactericidal activity at cellular level to prevent infections that could surface (Rowland and Niederweis, 2012). More so, deficiency and excessive intake of Cu had been reported to reduce the immune response in animal models including neutrophil numbers and its phagocytic activity (Yatoo *et al.,* 2013), lymphocytes proliferation and antigen-specific antibody production (Pocino *et al.,* 1991). Ruminants suffering from hypocuprosis had been reported with a lower lymphocyte count and decreased inflammatory responses to disease challenge (Zhou *et al.,* 2009),thus, they are more susceptible to infectious diseases and do not respond well to vaccination. Sharma *et al.* (2008) stated that the antimicrobial activity of the neutrophils was significantly influenced by Cu supplementation. Calves fed Cu supplemental diet had increased neutrophil activity compared with non-treated calves (Teixeira *et al.,* 2014). Thus, animals placed on adequate Cu nutrition tend to be less susceptible to infections. Cu supplementation has a direct influence on iron metabolism which was attributed to the role of ceruloplasmin (Cp), a copper-containing enzyme, α2-globulin with ferroxidase activity in the plasma thus, catalyzes the oxidation of the ferrous ion (Fe^{+2}) to ferric ion (Fe^{+3}) enabling Fe to be easily trapped by transferrin and then enhance haemoglobin (Hb) biosynthesis (Fox, 2003). Ceruloplasmin also helps to transport Cu, regulation of certain amines and its concentration across the system and this was said to be higher in Cu supplemented lambs (Senthilkumar *et al.*, 2009). More so, Cp is an alternative indicator used in determining Cu body status of (Underwood and Suttle, 1999). Hypocuprosis results to anaemia due to less release of iron leading to less availability of iron for erythropoiesis and many other functions. Cu is essential for the proper distribution, absorption and release of Fe throughout the body as earlier stated by Fox (2003). Thus, less Fe is available for erythropoiesis as a result of inadequate supply of Cu in the system. Copper enhances insulin function which enables cells to take in more glucose to be used for energy (Wang *et al.*, 1996).However, a reduction in albumin content and increased values of globulin was reported by Mudgal *et al.* (2008) and Mondal *et al.* (2004) respectively for Cu supplemented groups

Influence of copper supplementation on oxidative stress

Copper performs a key role in antioxidant system of the body by the virtue of its association in the enzymes Cu-Zn superoxide dismutase (SOD) and ceruloplasmin (ferroxidase).Antioxidant can be broadly defined as any substance that delays, prevents or remove oxidative damage from a target molecule (Halliwell and Gutteridge, 1995). Antioxidants can be broadly divided into enzymatic (Superoxide dismutase: SOD, Glutathione peroxidase: GSHPx and Catalase: CAT etc) and non-enzymatic (Vitamin E and Selenium etc). Glutathione(GSH) is a non-enzymatic antioxidant in both plant and animal; it is capable of preventing damage to important cellular component that could cause by reactive oxygen species (ROS) such as free-radicals, peroxide, lipid peroxide and heavy metals (Pompella *et al.,* 2003). The role of copper in reducing oxidative stress in livestock animals has been well established (Kleczkowski *et al.,* 2003). In the cytosol, Cu-Zn SOD enhances dismutation of superoxide radicals to hydrogen peroxide (Halliwell and Gutteridge, 1999). By the virtue of the fact that, copper is an antioxidant agent, it enhances anincrease in GSH and thereby facilitating theentering of copper into the cell and GSH significantly increases the copper intake rate thus, making morecopper available in the system as reported by Maryon *et al.* (2013). An increase in CAT has been reported to increase SOD with copper supplementation. The increase in the level of GSH also influenced the level of other enzymatic antioxidant (SOD and CAT) as the copper supplementation increased across the dietary treatments. Copper supplementation has been described by Solaiman *et al.* (2004) as an essential tool enhancing proper immune function in animals. More so, copper enhances the production of various enzymes like SOD as they exhibit their roles. Mohammed *et al.*(2015) reported SOD as the first line of defence and its role is to accelerate the dismutation of toxic superoxide produced during oxidative energy process to hydrogen peroxide. SOD has been found to influence phagocyte (immune cell) function in ruminant (Xin *et al.,* 1991). However, a reduction in SOD leads to oxidative damage of phagocytes therefore reducing their effectiveness in engulfing and removing pathogens in the system (Suttle and Jones, 1989). SOD and GSH are regarded as chain breaking antioxidant (Kokoglu *et al.,*2012), whose function is to receive an electron or donate an electron to a radical purposely to form stable products (Halliwell, 1995). A typical example of such chain reaction is lipid peroxidation, and this reaction will continue to produce until two radicals merge to form a stable product or the radicals are neutralized by a chain breaking antioxidant (De Zwart *et al.,* 1999). CAT is directly proportional to SOD such that an increase in SOD caused by copper supplementation led to an increase in CAT. Thus, hydrogen peroxide being an end product of superoxide ion dismutation would have been converted to water by CAT alongside with another enzymatic antioxidant; glutathione peroxidase (GPx) (Bourdel-Marchasson *et al.,*2001; Berr *et al.,*2004). More so, hydrogen peroxide is detoxified by CAT and GPxin animals. CAT protects cell from hydrogen peroxide emanated within the system and also play an important role in the acquisition of tolerance to oxidative stress in the adaptive response of cells. Thus, a balance between both the activities and intracellular levels of this antioxidant are the means for the survival of organisms and their health (Maydani *et al.,* 2001) through protective antioxidant systems.

Conclusion

Ruminants are predisposed to copper deficiency or low copper absorption due to complex nutritional interactions occurring in the rumen compartment. However, in order to overcome the constant negative influences on animal performance, copper supplementation in ruminant diet is required. Copper's role as a trace element in the animal system cannot be overstated; it boosts antioxidant defenses, which is essential for maintaining proper health and immune system. They are primarily responsible for the normal functioning of a variety of enzymes and proteins that are involved in a variety of physiological and biochemical processes. It also improves the metabolism of cholesterol, glucose, and iron in the body.

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