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EFFECTS OF MINERAL NUTRITION ON IMMUNE FUNCTION AND FACTORS THAT AFFECT TRACE MINERAL REQUIREMENTS OF BEEF CATTLE

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INTRODUCTION

Trace minerals exist in cells and tissues of the animal body in a variety of chemical combinations, and in characteristic concentrations, which vary with the trace mineral and tissue (McDowell, 1989, 1992; Underwood and Suttle, 1999). The concentrations of trace minerals must usually be maintained within quite narrow limits if the functional and structural integrity of the tissue is to be maintained and the growth, health, and productivity of the animal are to remain unimpaired (McDowell, 1989, 1992; Underwood and Suttle, 1999). Ingestion of diets that are deficient, imbalanced, or excessively high in trace minerals may induce changes in the form or concentration of the particular trace mineral in the body tissues and fluids, so that it falls below or rises above the tolerable limits. In such cases, biochemical lesions can develop, physiological functions may be adversely affected and structural disorders may arise, in ways which vary with the trace mineral, the degree and duration of the dietary deficiency or toxicity and the age, sex, or species of animal involved (McDowell, 1989, 1992; Underwood and Suttle, 1999). Certain homeostatic mechanisms in the body can be activated which delay or minimize the onset of such diet-induced changes. Ultimate prevention of the aforementioned changes require that the animal be supplied with a diet that is palatable and non-toxic and which contains the required minerals, vitamins, as well as other nutrients, in adequate amounts, proper proportions, and available forms (Underwood, 1971; Underwood and Suttle, 1999).

Trace mineral deficiencies, toxicities, and imbalances require the animal to metabolically compensate for the nutrient deviation. In doing so, certain metabolic diseases can manifest and immune function can be depressed, thus decreasing overall animal performance and health. The intent of this review is to discuss the function of trace minerals in health and immunity of livestock. For an in depth review of the effects of micronutrients on immunity see Galyean et al., (1999), and Spears (2000).

IMMUNE SYSTEM

The immune system is a remarkably adaptive defense system that has evolved in vertebrates to protect them from invading pathogenic microorganisms (Kuby, 1994). It is able to generate an enormous variety of cells and molecules capable of specifically recognizing and eliminating an apparently limitless variety of foreign invaders. These cells

and molecules act together in an adaptable dynamic network to protect the host (Kuby, 1994).

Immunity is the ability to resist infection. Immunity can be classified into two components: nonspecific and specific. Innate or nonspecific immunity refers to the basic resistance to disease that a species possesses. Innate immunity can be described as comprising four types of defensive barriers: 1) anatomic (skin), 2) physiologic (temperature, pH, oxygen tension), 3) phagocytic (ingestion of macromolecules by macrophages and neutrophils), and 4) inflammatory (vasodilatation and capillary permeability; Kuby, 1994). Acquired or specific immunity is immunity induced by exposure to an antigen, naturally or via vaccination (Kuby, 1994). Acquired or specific immunity can be further divided into two subcategories: humoral and cell mediated immunity. The humoral branch of the immune system involves the interaction of B cells with extracellular antigen and their subsequent proliferation and differentiation into antibody-secreting cells that are specific for a certain antigen. Antibodies secreted by B cells function as the effector of the immune humoral response by binding to an extracellular antigen and neutralizing and/or facilitating its elimination. Cell-mediated immunity involves the interaction of T cells and their associated cytokines to eliminate intracellular pathogens (Galyean et al., 1999).

Functionally, an immune response can be divided into two interrelated activities; recognition and response. The immune system is able to recognize subtle chemical differences that distinguish one foreign pathogen from another (Kuby, 1994). At the same time, the system is able to discriminate between foreign molecules and the body's own cells and proteins. Once a foreign protein is recognized, the immune system enlists the participation of a variety of cells and molecules to mount an appropriate response known as the effector response, which is uniquely suited to eliminate a specific type of pathogen (Kuby, 1994). Later exposure to the same foreign organism induces a memory response, characterized by a heightened immune response that serves to eliminate the pathogen and prevent disease. Overall, the basic function of the immune system in eukaryotes is to recognize self from non-self and thus prevent disease.

TRACE MINERALS

Trace minerals function primarily as catalysts in enzyme systems within cells. The roles that trace minerals play in enzymatic reactions range from weak, ionic strength effects to highly specific associations known as metalloenzymes (Underwood, 1971). Deficiencies and or imbalances of trace minerals can alter the activity of certain enzymes and function of specific organs thus impairing specific metabolic pathways as well as overall immune function.

Zinc:

Zinc is an essential component of numerous enzymes and is part of the structure of many proteins. Zinc containing enzymes are found in all parts of the major metabolic pathways involved in carbohydrate, lipid, protein, and nucleic acid metabolism, epithelial tissue integrity, cell repair and division, and vitamin A transport and utilization (Kaneko, 1989).

Numerous experiments with humans and laboratory animals have indicated that zinc deficiency reduced immune response and disease resistance (Chesters, 1997). However, there is little research in ruminants examining the influence of zinc deficiency on immune function and disease resistance (Spears, 2000). Lambs fed a semi-purified diet severely deficient in zinc showed a reduced blastogenic response to PHA (a T-cell mitogen), but an increased response to PWM, a T-dependent B-cell mitogen (Droke and Spears, 1993). Zinc deficient lambs also had a lower percentage of lymphocytes and a higher percentage of neutrophils in their blood. Inflammatory response to PHA was also similar in zinc-adequate and zinc-deficient lambs. Furthermore, zinc-deficient cattle showed similar cell-mediated and humoral immune responses as zinc adequate cattle (Spears and Kegley, unpublished data). However, Engle et al. (1995) reported a greater skin swelling response in zinc adequate calves when compared to marginally zinc-deficient calves.

Although the data is limited and variable on the effects of marginal zinc deficiency on immune function, Galyean et al. (1995) reported that increasing the level of supplemental zinc from 30 to 100 mg/kg diet tended to reduce morbidity from respiratory diseases in newly weaned stressed (by transport) calves.

Copper:

Animals require copper for a number of enzymes (cytochrome oxidase, lysyl oxidase, superoxide dismutase, dopamine- β -hydroxylase, tyrosinase, and ceruloplasmin) that are involved in an array of important body functions such as cellular respiration, bone formation, proper cardiac function, tissue development, myelination of the spinal cord, keratinization, tissue pigmentation, and lipid metabolism. Understanding how copper functions in the aforementioned enzymes can help to explain the clinical signs observed during a copper deficiency.

Prohaska and Failla (1993) have conducted several studies in rats and mice which have indicated that both cell mediated and humoral immunity are greatly depressed by copper deficiency. However, studies in domestic livestock have failed to show consistent effects of copper deficiency on either cell-mediated or humoral immune response (Spears, 2000).

Severe copper deficiency induced by feeding a semi-purified diet low in copper did not affect *in vitro* mitogen induced lymphocyte blastogenesis (Stabel et al., 1993; Ward et al., 1997). Furthermore, the addition of 5 mg Mo/kg to the semi-purified diet to produce a more severe copper deficiency did not reduce lymphocyte blastogenic response to PHA or PWM (Ward et al., 1997). However, recently Wright et al., (2000) indicated that low copper status in steers was associated with a reduced response of peripheral-blood lymphocytes to stimulation with T cell-mitogens following weaning and IBRV challenge.

From the more basic molecular immune research it is clear that copper plays an important role in the immune response. However, the reason for the variable responses of copper supplementation on immune responses in livestock is unclear. There are many factors that could affect an animal's response to copper supplementation such as the duration and

concentration of copper supplementation, the absence or presence of dietary copper antagonists (sulfur and molybdenum), environmental factors, and breed differences in copper metabolism.

Selenium:

Selenium was first identified in the 1930's as a toxic element to some plants and animals. However, selenium is now known to be required by laboratory animals, food animals, and humans (McDowell, 1992) for proper growth and immune function. In 1973, Rotruck et al. reported that selenium functions as a component of glutathione peroxidase, an enzyme that inactivates oxygen radicals such as hydrogen peroxide and prevents them from causing cellular damage.

Since the discovery by Rotruck et al. (1973) selenium has been shown to affect specific components of the immune system (Mulhern et al., 1985). Earlier research by Reffett et al. (1988) reported lower serum IgM (an antibody produced by B cells) concentrations and anti-IBRV titers in selenium deficient calves challenged with infectious bovine rhinotracheitis virus than when compared to selenium adequate calves. Polymorphonuclear leukocyte function was reduced in goats (Aziz et al., 1984) and cattle (Gyang et al., 1994) fed selenium-deficient diets compared with controls receiving selenium-adequate diets. Some studies have shown increased T-lymphocyte blastogenesis following *in vitro* stimulation with mitogen but others have not (Spears, 2000). Recently, bovine mammary endothelial cells growing in selenium-deficient cell culture media were found to exhibit enhanced neutrophil adherence when stimulated with cytokines (Maddox et al., 1999; Spears, 2000). These findings may indicate that selenium could affect neutrophil migration into tissues and subsequent inflammation.

Chromium:

Chromium was first shown to be essential for mammals by Schwarz and Mertz (1959). Since then, chromium has been shown to influence carbohydrate metabolism (Mertz, 1993), lipid metabolism (Abraham et al., 1991), and protein absorption and metabolism (Okada et al., 1983; Kornegay et al., 1997).

Highly variable responses to chromium supplementation have made it difficult to determine the specific effect of chromium on the immune system (Spears, 2000). Burton et al. (1994) reported that in newly weaned stressed feedlot calves, chromium supplementation at .5 mg of chromium/kg diet for 30 days post-transit to the feedlot increased the magnitude of peak antibody titer response to IBR vaccination but had no effect on antibody titers to IP-3 vaccination relative to the unsupplemented controls. Dairy cows supplemented with 0.5 mg of chromium/kg diet had greater primary and secondary antibody responses to immunization of an ovalbumin antigen than control cows but had similar antibody responses to human erythrocytes antigen immunization (Burton et al., 1993). It is unclear as to why the chromium effects were observed with one antigen and not the other. Furthermore, the addition of 0.4 mg of chromium/kg diet did not affect antibody titer responses to porcine erythrocyte immunization in stressed cattle (Kegley et al., 1997). Inconsistent immune responses to chromium supplementation have also been observed in swine (van Heugten and Spears, 1997) and sheep (Gentry et al., 1999).

The reason for the variable responses of chromium supplementation on immune responses in domesticated livestock species is unclear. Factors that may contribute to the inconsistent findings between studies may include: 1) the initial chromium status of the animals; 2) the amount of available chromium in the control diet; 3) the form of chromium supplemented; and 4) the type or degree of stress imposed on the animals (Spears, 2000).

SUMMARY

The interactions between trace minerals, immunology, and disease resistance are extremely complex. From the more basic molecular immune research it is clear that trace minerals play an important role in the immune response. Despite the apparent involvement of certain trace minerals in the immune system, deficiencies of trace minerals have not always increased the susceptibility of domesticated livestock species to natural or experimentally-induced infections (Spears, 2000). There are many factors that could affect an animal's response to trace mineral supplementation such as the duration and concentration of trace mineral supplementation, physiological status of an animal (pregnant vs. open), the absence or presence of dietary antagonists, environmental factors, and the influence of stress on trace mineral metabolism. Breed differences in trace mineral metabolism have also been documented (Weiner et al., 1978; Gooneratne, et al., 1994; Ward et al., 1995; Du et al., 1996; Mullis et al., 1997). Furthermore, research has indicated that different breeds of cattle respond differently to the same immune challenge (Schultz et al., 1971; Blecha et al., 1984; Engle et al., 1999). This may, in part, be related to differences in trace mineral metabolism between different breeds of cattle. Future research is warranted to determine the effects of trace minerals on immune response and disease resistance in livestock.

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