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Role of antioxidants and trace elements in health and immunity of transition dairy cows

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Abstract

A number of antioxidants and trace minerals have important roles in immune function and may affect health in transition dairy cows. Vitamin E and β-carotene are important cellular antioxidants. Selenium (Se) is involved in the antioxidant system via its role in the enzyme glutathione peroxidase. Inadequate dietary vitamin E or Se decreases neutrophil function during the perparituritent period. Supplementation of vitamin E and/or Se has reduced the incidence of mastitis and retained placenta, and reduced duration of clinical symptoms of mastitis in some experiments. Research has indicated that β-carotene supplementation may enhance immunity and reduce the incidence of retained placenta and metritis in dairy cows. Marginal copper deficiency resulted in reduced neutrophil killing and decreased interferon production by mononuclear cells. Copper supplementation of a diet marginal in copper reduced the peak clinical response during experimental *Escherichia coli* mastitis. Limited research indicated that chromium supplementation during the transition period may increase immunity and reduce the incidence of retained placenta.
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Introduction

The transition or periparturient period, from 3 weeks before to 3 weeks after parturition, is a stressful time for dairy cows (Drackley, 1999). During the transition period, immunosuppression commonly occurs and cows exhibit great susceptibility to a number of diseases (Mallard et al., 1998). A number of components of the host defense system are altered during this period including neutrophil function, lymphocyte responsiveness to mitogen stimulation, antibody responses, and cytokine production by immune cells (Mallard et al., 1998; Kehrli et al., 2006). Impaired neutrophil function prior to parturition has been linked to the occurrence of mastitis, metritis, and retained placenta in dairy cows (Cai et al., 1994; Kimura et al., 2002).

Impaired immune responses observed in periparturient dairy cows may relate to the stresses of late pregnancy and parturition stimulating release of stress hormones such as corticosteroids (Sordillo, 2005). Oxidative stress in transition cows may also be a contributory factor to increased disease susceptibility (Miller et al., 1993). Metabolic demands associated with late pregnancy, parturition, and initiation of lactation would be expected to increase the production of reactive oxygen species (ROS) (Sordillo, 2005). Oxidative stress occurs when the production of ROS exceeds the antioxidant defense mechanisms present in the body. Reactive oxygen species can initiate lipid peroxidation and cause cellular damage to tissues. Immune cells are particularly sensitive to oxidative stress because (1) their membranes contain high concentrations of polyunsaturated fatty acids that are very susceptible to peroxidation, and (2) they produce large amounts of ROS when stimulated.

A number of vitamins and trace minerals are involved in the antioxidant defense system and a deficiency of any of

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these nutrients may depress immunity in transition cows. Vitamin E is an important antioxidant that has been shown to play an important role in immunoresponsiveness and health in dairy cows (Weiss and Spears, 2006). β-Carotene can also function as an antioxidant and can affect immune responses (Chew and Park, 2004). A number of trace minerals are required for functioning of enzymes involved in the antioxidant defense system. Certain trace minerals may also affect immune cells via mechanisms distinct from antioxidant properties.

Recent reviews have focused on the role of trace minerals and vitamins in immune function and disease resistance in ruminants (Spears, 2000; Weiss and Spears, 2006). This paper will review the role of antioxidants and trace minerals on immunity and health in the transition cow.

Vitamin E

Vitamin E is an important lipid soluble antioxidant that protects against free radical-initiated lipid peroxidation (Halliwell and Gutteridge, 1999). Fresh green forage is an excellent source of vitamin E. However, concentrates and stored forages (hays, haylages, and silages) are generally low in vitamin E (NRC, 2001).

A number of studies (Goff and Stable, 1990; Weiss et al., 1990; Politis et al., 1995) have documented that plasma concentrations of α-tocopoherol or vitamin E can decrease dramatically in dairy cows fed stored forages during the periparturient period. In these studies cows were fed alfalfa hay (Goff and Stable, 1990), corn silage and alfalfa hay (Weiss et al., 1990), or a combination of corn silage, hay, and haylage (Politis et al., 1995) as the forage source. The lowest plasma α-tocopherol concentrations are generally observed between 1 week pre-partum and 2 weeks post-partum. In cows fed stored forages, relatively high supplemental levels of vitamin E (3000–4000 IU/day) are needed to prevent the drop in plasma α-tocopherol concentrations around parturition (Politis et al., 1996; Weiss et al., 1997). Dairy cows fed stored forages require approximately 1.6 IU of supplemental vitamin E/kg BW (approximately 80 IU/kg DM intake) during the dry period to maintain plasma α-tocopherol at concentrations (approximately 3.0 μg/mL) that maximize health and immune function (NRC, 2001). This level of supplemental vitamin E will mitigate but not totally prevent a drop in plasma α-tocopherol around parturition (Weiss et al., 1997).

Immunity

The major impact of vitamin E on immunity appears to relate to enhanced neutrophil function. Oral or parenteral administration of vitamin E in periparturient dairy cows generally has not affected neutrophil phagocytic activity but has improved the ability of blood neutrophils to kill ingested bacteria (Hogan et al., 1990, 1992). Supplementation of 3000 IU of vitamin E/day during the transition period prevented a decline in neutrophil superoxide anion production and interleukin 1 (IL-1) production after parturition compared with control cows not supplemented with vitamin E (Politis et al., 1995). Rapid recruitment of neutrophils is critical for maximizing host defense mechanisms. Vitamin E supplementation at 3000 IU/day prevented a decrease in chemotactic responsiveness of neutrophils beginning at 2 weeks prior to and continuing for 4 weeks after parturition (Politis et al., 1996). Limited research suggests that vitamin E may enhance chemotaxis by increasing receptor-bound urokinase–plasminogen activator in neutrophils (Politis et al., 2001).

Production of IL-1 and major histocompatibility (MHC) class II antigen expression by blood monocytes were improved by vitamin E supplementation (Politis et al., 1995). However, measures of mammary macrophage function have not been affected by vitamin E in periparturient cows (Politis et al., 1995, 1996). Vitamin E supplementation during the transition period also did not affect lymphocyte blastogenic responses to stimulation with concanavalin A (Con A), a T-cell mitogen (Politis et al., 1995).

Health

It is well documented that the functions of vitamin E and selenium (Se) are related and that animal responses to supplementation of either nutrient can depend on the nutritional status of the other nutrient (Weiss and Spears, 2006). Supplementing 740 IU vitamin E/day throughout the dry period reduced incidence of clinical mastitis by 37% and duration of mammary infections by 44% in cows fed a diet low in Se (Smith et al., 1984). Control cows in this study had a 41% incidence of clinical mastitis and a 0.41 month duration of infection per quarter lactating (Smith et al., 1984). Weiss et al. (1997) reported that supplementing 4000 IU of vitamin E/day for 14 days pre-partum reduced new intramammary gland infections and incidence of clinical mastitis in early lactation by 63% and 89%, respectively, compared to control cows fed 100 IU/day. Incidence of clinical mastitis in cows fed 100 IU of vitamin E/day in this study was approximately 27%. Supplementation of cows in this study with 1000 IU of vitamin E/day was less effective (30% vs. 89% reduction) in preventing mastitis than 4000 IU/day (Weiss et al., 1997). In this study all cows were supplemented with 0.1 mg Se/kg diet, a level that would be considered low or marginal relative to requirements. In contrast, Batra et al. (1992) found that supplementation with 1000 IU of vitamin E/day did not affect incidence of clinical mastitis in dairy cows fed diets low in Se (0.10–0.12 mg Se/kg in the diet). Differences in Se status may explain the discrepancy in response to vitamin E between these studies (Batra et al., 1992; Weiss et al., 1997). Plasma Se concentrations in cows were much lower in the Batra et al. (1992) study.

Incidence of retained placenta also has been reduced by oral (Miller et al., 1993) or intramuscular (IM) administration of vitamin E but responses have been variable (Allison and Laven, 2000). Erskine et al. (1997) found that IM injection of 3000 IU of vitamin E pre-partum reduced the incidence of metritis as well as retained placenta in dairy cows. LeBlanc et al. (2002) reported that responses of dairy cows to a subcutaneous injection of 3000 IU of vitamin E, one week before expected calving, was dependent on pre-treatment vitamin E status. Vitamin E administration reduced the incidence of retained placenta in cows with marginal pre-treatment α-tocopherol concentrations (serum α-tocopherol to cholesterol mass ration $<2.5 \times 10^{-3}$) but not in cows with adequate serum α-tocopherol concentrations.

Selenium (Se)

The Se requirement of dairy cattle is approximately 0.3 mg/kg diet (NRC, 2001). Although the requirement for Se is relatively low, feedstuffs produced in many areas of the world contain considerably less than 0.3 mg/kg, necessitating the need for supplementation. Selenium functions in the antioxidant system as an essential component of a family of glutathione peroxidase enzymes. These enzymes destroy hydrogen peroxide and also lipid hydroperoxides. Thioredoxin reductase is another selenoenzyme that may function to prevent oxidative stress (Mustacich and Powis, 2000).

Immunity

Selenium deficiency in dairy cows reduced the ability of blood (Hogan et al., 1990) and milk neutrophils (Grasso et al., 1990) to kill bacteria. Chemotactic migration of neutrophils was reduced by Se deficiency in goats (Aziz et al., 1984) and in vitro addition of Se to bovine neutrophils and macrophages has enhanced their migration (Ndiweni and Finch, 1995, 1996). Bovine mammary endothelial cells grown in Se-deficient cell culture media were found to exhibit enhanced neutrophil adherence when stimulated with tumor necrosis factor (TNF)-α, IL-1, or hydrogen peroxide (Maddox et al., 1999). They suggested that Se deficiency may cause tight adhesion between neutrophils and endothelial cells, and hinder neutrophil migration to the infection site. In dairy cows, whole blood Se concentrations were positively correlated with neutrophil adhesion (Cebra et al., 2003).

Dietary Se can also affect cell-mediated immunity in dairy cows (Cao et al., 1992). Peripheral blood lymphocytes isolated from Se-deficient cows exhibited a reduced response to mitogen stimulation with Con A. Impaired response of lymphocytes from Se-deficient cows may be related to altered arachidonic acid oxidation by lymphocytes via the 5-lipooxygenase pathway (Cao et al., 1992). Lymphocytes from deficient cows produced less products of arachidonic acid oxidation when stimulated, specifically 5-hydroxyeicosatetraenic and leukotriene B_4.

Health

Blood concentrations of Se or glutathione peroxidase activities in dairy herds have been related to mammary gland health in several studies (Erskine et al., 1987; Weiss et al., 1990; Jukola et al., 1996). Whole blood Se concentration and glutathione peroxidase activity were negatively related to prevalence of intramammary infection in a study involving 32 dairy herds in Pennsylvania (Erskine et al., 1987). High serum Se concentrations were associated with reduced rates of mastitis and lower bulk-tank somatic cell counts in Ohio dairy herds (Weiss et al., 1990).

Smith et al. (1984) evaluated the effects of supplemental Se and/or vitamin E on mastitis in cows fed diets low in both Se and vitamin E. Administration (IM) of 0.1 mg Se/kg BW at 21 days before calving did not affect the incidence of clinical mastitis but reduced the duration of clinical symptoms in cows with clinical mastitis by 46%. Selenium administration in combination with oral supplementation of vitamin E (740 IU/day) was most effective, reducing incidence of mastitis and duration of clinical symptoms by 37% and 62%, respectively (Smith et al., 1984). In this study, mastitis was caused by environmental pathogens (Coliform and *Streptococcus*) and not *Staphylococcus aureus*. Dietary Se supplementation to diets deficient in Se (unknown vitamin E status) reduced the rate of new intramammary gland infections in dairy cows (Malbe et al., 1995). Experimental mastitis, induced by intramammary challenge with *Escherichia coli* was more severe and of longer duration in cows receiving 0.04 mg Se/kg diet compared with those receiving 0.14 mg Se/kg diet (Erskine et al., 1989). Following intramammary challenge with *S. aureus*, Selenium-deficient cows had greater peak bacteria concentrations in milk than Se-supplemented cows (Erskine et al., 1990) However, the severity and duration of infection was not affected by dietary Se in this study.

Numerous studies (Allison and Laven, 2000) have indicated that pre-partum Se supplementation can reduce the incidence of retained placenta in dairy cows fed diets low in Se. Failure of supplemental Se in some studies to affect the incidence of retained placenta can be explained by the control diets being adequate in Se (Schingoethe et al., 1982; Allison and Laven, 2000). Most studies have involved IM administration of Se in combination with vitamin E. However, Julien et al. (1976) found that oral Se supplementation was as effective as IM administration of Se and vitamin E in preventing retained placenta in cows fed Se-deficient diets. Cows with retained fetal membranes had lower glutathione peroxidase activity in maternal and placental tissues than cows without retained placenta (Kankofer et al., 1996).

Copper (Cu)

Copper is involved in the antioxidant system via its involvement in the enzymes Cu–Zn superoxide dismutase (SOD) and ceruloplasmin. Copper–Zn SOD is responsible for dismutation of superoxide radicals to hydrogen peroxide in the cytosol (Halliwell and Gutteridge, 1999). Ceruloplasmin is a Cu transport protein that also exhibits oxidase activity. It oxidizes ferric iron (Fe^{+3}) to ferrous iron (Fe^{+2})

without the production of free Fe^{+3} that can cause oxidation and peroxidation to tissues (Halliwell and Gutteridge, 1999). Ceruloplasmin is an acute phase protein that increases during disease and may be important in scavenging superoxide radicals (Broadley and Hoover, 1989).

Copper deficiency in cattle is generally due to the presence of dietary antagonists, such as sulfur, molybdenum and iron (Fe) that reduce Cu bioavailability (Spears, 2003). Dietary requirements for Cu are greatly increased by high concentrations of molybdenum and sulfur.

Immunity

Considerable research has indicated that dietary Cu affects phagocytic as well as specific immune function (Spears, 2000; Weiss and Spears, 2006). However, limited research with dietary Cu and immunity has been conducted in periparturient dairy cows. Torre et al. (1995, 1996) evaluated the effect of dietary Cu on immune function in Holstein heifers. Heifers were fed a control diet containing 6–7 mg Cu/kg diet or the control diet supplemented with 20 mg Cu/kg diet beginning at 84 days pre-partum and continuing into lactation. Neutrophils from heifers fed the low Cu diet exhibited reduced killing of *S. aureus* when blood samples were collected at approximately 35 days post-partum (Torre et al., 1996). Phagocytic activity of neutrophils was not affected by Cu status. Mononuclear cells from heifers were evaluated at approximately 90 days of lactation. Responses of mononuclear cells to mitogen stimulation were not affected by dietary Cu (Torre et al., 1995). However, mononuclear cells from heifers receiving the low Cu diet produced less interferon when stimulated with Con A than cells isolated from cows supplemented with 20 mg Cu/kg diet. Production of IL-2 by mononuclear cells was not affected by dietary Cu.

Health

Heifers fed diets marginal in Cu (6–7 mg/kg diet) had a greater percentage (60% vs. 36%) of infected quarters at calving than heifers supplemented with 20 mg Cu/kg diet (Harmon, 1998). In a separate study, heifers were fed a basal diet (6–7 mg Cu/kg) or the basal diet supplemented with 10 mg Cu/kg diet from either Cu proteinate or Cu sulfate for 120 days prior to parturition (Harmon, 1998). Heifers supplemented with Cu proteinate had a greater proportion of uninfected quarters at calving compared with heifers fed the control or Cu sulfate supplemented diet. However, in this study, heifers supplemented with either Cu source had a slightly higher percentage of quarters infected with major pathogens than heifers fed the low Cu diet.

Scaletti et al. (2003) evaluated the effect of dietary Cu on responses of heifers to an intramammary *E. coli* challenge at 34 days of lactation. Heifers were fed a control diet (6.5 mg Cu/kg) or the control diet supplemented with 20 mg Cu/kg from 60 days pre-partum through 42 days of lactation. Following the *E. coli* challenge, heifers supplemented with Cu had lower *E. coli* numbers and somatic cell counts in milk, lower clinical scores, and lower peak rectal temperatures than controls. Although the severity of *E. coli* infection was decreased by supplemental Cu, the duration of infection was not affected by Cu (Scaletti et al., 2003). Possible effects of dietary Cu on susceptibility of cows to other diseases during the transition period have not been investigated.

Chromium (Cr)

The primary role of Cr appears to relate to its ability to enhance the action of insulin. Requirements for Cr in dairy cattle have not been defined (NRC, 2001). However, studies have indicated that Cr supplementation may affect health and immune response in stressed calves (Spears, 2000). Several other reports also indicate that Cr supplementation can significantly affect feed intake and milk production in early lactation dairy cows (Hayirli et al., 2001; McNamara and Valdez, 2005; Smith et al., 2005). In these studies Cr was supplemented from 21 to 28 days pre-partum until 28 to 35 days post-partum.

Immunity

Studies in periparturient dairy cows indicate that Cr supplementation of practical diets may affect cell-mediated and humoral immune responses. Lymphocytes from cows supplemented with 0.5 mg Cr (Cr-amino acid chelate)/kg diet had increased blastogenic responses to Con A stimulation (Burton et al., 1993). Furthermore, Cr supplementation prevented the decrease in blastogenic response that was observed in control cows 2 weeks pre-partum. Mononuclear cells from dairy cows supplemented with 0.5 mg Cr/kg diet produced lower concentrations of cytokines (IL-2, interferon, and TNF-α) following stimulation with Con A than control cows (Burton et al., 1996). Chromium supplementation also improved primary and secondary antibody responses to ovalbumin administration but not antibody responses to injection of human erythrocytes (Burton et al., 1993). The primary injection of ovalbumin and human erythrocytes was given 2 weeks before parturition and the secondary injection was administered 2 weeks post-partum. Supplementation with 5 mg Cr/day increased antibody responses following vaccination with tetanus toxin in dairy cows (Faldyna et al., 2003). Neutrophil function has not been affected by dietary Cr (Chang et al., 1996; Faldyna et al., 2003).

Health

Research examining the effects of dietary Cr on health in dairy cows is limited. Chromium supplementation, from a Cr-amino acid chelate, pre-partum and during the first 16 weeks of lactation did not affect mammary gland health status (Chang et al., 1996). Supplementing 3.5 mg Cr (from

Cr picolinate) during the last 9 weeks of pregnancy reduced (16% vs. 56%) the incidence of retained placenta in dairy cows (Villalobos-F et al., 1997).

Zinc (Zn)

Zinc is an essential component of numerous enzymes including enzymes involved in the synthesis of DNA and RNA. In the antioxidant system Zn is a component of Cu–Zn SOD. Zinc also induces synthesis of metallothionein, a metal binding protein that may scavenge hydroxide radicals (Prasad et al., 2004). In addition to an antioxidant role, Zn may affect immunity via its important role in cell replication and proliferation (Weiss and Spears, 2006).

Immunity

Research in humans and laboratory animals has documented that Zn deficiency impairs immune responses and reduces disease resistance (Shankar and Prasad, 1998). Severe Zn deficiency in calves (Perryman et al., 1989) and in lambs (Droke and Spears, 1993) has also been shown to impair immunity. In cattle fed practical diets marginal deficiency is more likely to occur than severe Zn deficiency. Controlled studies with growing cattle (Spears and Kegley, 2002) and lambs (Droke and Spears, 1993) suggest that marginal Zn deficiency does not impair cell-mediated or humoral immune responses. Plasma Zn concentrations decrease in dairy cows at parturition and return to baseline values within 3 days (Goff and Stable, 1990). However, the effect of dietary Zn on immune function in periparturient cows has received little attention.

Health

Some research suggests that organic forms of Zn may affect mammary gland health status. Supplementation of dairy diets with Zn methionine has reduced somatic cell counts in some studies but not in others (Kellogg, 1990). Spain (1993) reported that lactating cows supplemented with Zn proteinate had a lower rate of new intramammary infections than those supplemented with inorganic Zn oxide. He suggested that Zn proteinate may enhance resistance to mammary infections by increasing keratin synthesis in the teat canal.

β-Carotene

β-Carotene is the major precursor of vitamin A and occurs naturally in feedstuffs. Independent of its role as a source of vitamin A, β-carotene may affect immune function. In fact, carotenoids without vitamin A activity have also been found to enhance immune response (Chew and Park, 2004). β-Carotene can react with singlet oxygen and serve as a lipid soluble antioxidant.

Immunity

Supplementation of periparturient cows with 300 or 600 mg β-carotene/day enhanced lymphocyte proliferation induced by mitogen stimulation before and after parturition (Michal et al., 1994). Addition of low concentrations of β-carotene to bovine lymphocyte cultures also stimulated mitogen-induced proliferation (Daniel et al., 1991). Neutrophil function has not been consistently affected by β-carotene supplementation (Michal et al., 1994).

Health

Dairy cows supplemented with β-carotene around dry-off had lower rates of new mammary gland infections during early dry-off (Chew, 1993). In dairy cows supplemented with 50,000 IU of vitamin A/day, neither increasing supplemental vitamin A nor the addition of 300 mg β-carotene/day affected the incidence of clinical mastitis or new intramammary infections (Oldham et al., 1991). Michal et al. (1994) evaluated the effects of β-carotene and vitamin A supplementation on the incidence of retained placenta and metritis in dairy cows. Control cows received no supplemental vitamin A in this study. Supplementation of either β-carotene (300 or 600 mg/day) or vitamin A (120,000 IU/day) significantly reduced incidence of retained placenta compared to control cows. Incidence of metritis was significantly reduced by β-carotene but not by vitamin A supplementation.

Conflict of interest statement

Neither of the authors (Jerry W. Spears and William P. Weiss) has a financial or personal relationship with people or organisations that could inappropriately influence or bias the paper entitled *Role of antioxidants and trace elements in health and immunity of transition dairy cows*.

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