

Enhancing Immunity and Disease Resistance of Dairy Cows through Nutrition

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Introduction

The immune system is the animal's defense system against pathogens and any other non-self molecules that may enter the animal. As with other species, dairy cows are susceptible to a wide range of diseases caused by infectious organisms. In addition to the damage and perturbed metabolism caused directly by these pathogens, the immune response itself can insult animal health and well-being, mostly due to excessive inflammation. Pathogenic infection and inflammatory damage can happen at any time, but there is an increased number and severity of infections around the time of calving that are partially due to a weakened immune system; this weakened immune system is often termed immunosuppression or immune dysfunction. This immune dysfunction is not limited to isolated immune variables; rather it is broad in scope and affects multiple functions of various immune cell types (Sordillo and Streicher, 2002). The combined results of these impairments are that cows may be hyposensitive and hyporesponsive to antigens, and therefore more susceptible to infectious disease such as mastitis during the periparturient period (Mallard et al., 1998). Grommers et al. (1989) reported that fewer mammary quarters responded to *E. coli* endotoxin, and maximum somatic cell count also was somewhat later and less pronounced during early lactation than during mid-lactation. This later, more subdued phagocytic response to a bacterial infection, may allow for a greater multiplication of bacteria within the tissue, thereby resulting in more severe infection (Shuster et al., 1996).

Consequences of Impaired Immunity

Infectious disease detracts from farm profitability through decreased production efficiency and increased morbidity and mortality. Infections of the mammary gland (mastitis) or uterus (metritis) are common sources of inflammation in lactating cows, particularly during the periparturient period. Mastitis has been reported to reduce lactation milk yield by almost 600 kg (Rajala-Schultz et al., 1999) and is also an important risk factor for involuntary culling (Grohn et al., 1988). Other health disorders common during this period (e.g., milk fever and ketosis) do not arise from infectious organisms, but instead have metabolic origins. As one example, Rajala-Schultz et al. (1999) reported single cases of clinical ketosis reduced milk yields by about 500 kg. Although the etiologies of infectious and metabolic disorders differ, epidemiologists

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report a significant association between their occurrences. For example, Curtis et al. (1985) reported that cows with milk fever were more than 5 times as likely to contract clinical mastitis as animals without milk fever. These results do not imply cause and effect; however, they suggest an association between the occurrences of one disease with that of a second disorder. Potential causal relationships between periparturient metabolism and immune function have been investigated for about the last 20 years, but this research has intensified recently.

Immune Dysfunction: Why do we care?

We care about a poorly functioning immune system because it means that periparturient cows are more like to become infected with a new organism, have a chronic subclinical infection escalate to become clinical, or have an infection that would otherwise be fairly minor, become more severe. Wilson et al. (2004) reported that if cows were to have clinical mastitis at any point during a lactation, it was much more likely for both, primiparous and multiparous cows to present that infection during the first week postpartum than at any other time during the subsequent months. Certainly some of these infections in early lactation cows were contracted during the dry period, but it is likely that immunosuppression contributed to both new infections and also contributed to chronic infections spiking around the time of calving. Indeed, Shuster et al. (1996) inoculated early- or midlactation cows with identical numbers of *E. coli* into one mammary quarter and reported that periparturient cows experienced a more rapid growth of bacteria, a more severe infection, and displayed greater pyrexia than midlactation cows. Practically speaking, those who work with dairy cows for a living realize the potentially fatal consequences of coliform mastitis immediately postpartum compared to coliform infections later in lactation. More numerous and more severe infections are hallmarks of periparturient immunosuppression.

Effects of Metabolism on Immunocompetence

The cause of periparturient immunosuppression is not known, but is the subject of much research. Research to date suggests that this immune dysfunction appears to be due to a combination of endocrine and metabolic factors. Glucocorticoids (e.g. cortisol), known endocrine immunosuppressants, are elevated around the time of calving, and have been postulated to be at least partly responsible for periparturient immunosuppression (Burton et al., 1995). Although the period of elevated cortisol at calving is of short duration for many cows, Nikolić et al. (2003) displayed the variability of periparturient cortisol levels on an individual cow basis. It is likely that elevated cortisol concentrations or a longer duration of glucocorticoid exposure at the time of calving is not beneficial to immune function. The calving process and environmental conditions should be carefully managed to minimize physiological perturbances and external stressors. In addition to periparturient changes in glucocorticoids, changes in estradiol and progesterone just prior to calving may directly or indirectly affect immunocompetence (Weber et al., 2001). However, changes in any of these steroid hormones do not overlap with the entire period of immunosuppression, suggesting that other causes are at least partially responsible for immune dysfunction.

Periparturient negative energy balance has been implicated in contributing to immunosuppression. Perhaps one of the most convincing experiments implicating the metabolic demand of lactation on impaired immunity utilized the mastectomized cow model (Kimura et al., 1999). In this experiment, the presence of the mammary gland (vs. mastectomized cows) and its attendant metabolic demands slowed recovery of neutrophil function postpartum, suggesting that fuel use, metabolite concentrations, or endocrine profiles associated with lactation exacerbated periparturient immunosuppression (Kimura et al., 1999). Furthermore, associative studies have linked lower prepartum dry matter intake with either reduced immune function (Hammon et al., 2006) or increased severity of inflammatory disease postpartum (Huzzey et al., 2007).

It stands to reason that if negative nutrient or energy balance around the time of calving was a significant cause of periparturient immunosuppression, it should be possible to recreate immune dysfunction in virtually any cattle class using experimental feed restriction models. Experimental induction of immunosuppression would help to prove causality of periparturient dysfunction, but would also yield valuable help in our research of this problem - less expensive animal models could be used and greater experimental flexibility would be created without depending on the (unknown) exact day of an expected calving. However, research results using feed restriction models have been largely disappointing; few experiments have resulted in widespread immunological changes mimicking those seen around the time of natural parturition in dairy cows. Experimentally-induced negative energy balance alone had little effect on the expression of adhesion molecules on the surface of bovine leukocytes (Perkins et al., 2001). Furthermore, experimental negative energy balance in midlactation cows did not affect the clinical symptoms associated with an intramammary endotoxin infusion (Perkins et al., 2002). Similarly, Moyes et al. (2009a) reported only minor differences in immunocompetence of post-peak cows subjected to nutrient restriction for 5 d prior to intramammary experimental mastitis. The disagreement between experimental models of nutrient restriction and periparturient dairy cows suggests that other variables during the periparturient period are more likely responsible for immunosuppression than just nutrient balance or transient changes in circulating metabolites.

Relating to metabolites, other work has investigated individual metabolic components associated with negative energy balance; specifically, ketones, and more recently, nonesterified fatty acids have been the most studied. Kremer et al. (1993) reported that experimental mastitis was more severe in ketotic than non-ketotic cows, and as reviewed by Suriyasathaporn et al. (2000), ketosis may increase the risk of mastitis in periparturient immunosuppressed cattle because many immune cell types are negatively affected by metabolite levels typical of a ketotic environment (i.e., low concentrations of glucose and high concentrations of ketone bodies and NEFA). Other studies have suggested that it is the NEFA, not the ketones per se, that are responsible for the negative postpartum immune influences. Ster et al. (2012) reported that in vitro concentration of NEFA equivalent to that reported in periparturient cows in vivo, decreased peripheral blood mononuclear cell proliferation and also polymorphonuclear neutrophil (PMN) respiratory burst activity. This study lends support to that of Scalia et

al. (2006), wherein in vitro incubation of PMN with NEFA resulted in decreased PMN function and viability. These laboratory experiments are consistent with field experiments suggesting that elevated levels of NEFA and (the ketone) beta-hydroxybutyrate around the time of calving are predictive for subsequent clinical mastitis (Moyes et al., 2009b) and the development of displaced abomasum, clinical ketosis, metritis and retained placenta (Ospina et al., 2010). From a practical standpoint, strategies that have been reported to help manage periparturient energy metabolites, such as maintaining moderate periparturient body condition scores (Lacetera et al., 2005) and not overfeeding during the prepartum period (Graunard et al., 2012), appear beneficial to immune function around the time of calving.

Another aspect of periparturient metabolism that has the potential to impact immune competence is calcium metabolism. Significant quantities of calcium are required for milk synthesis and an inadequate adaptation to this calcium sink at the onset of lactation results in hypocalcemia (milk fever). Although it is important for milk synthesis, calcium is also important for intracellular metabolism and signaling in most cell types, including the leukocytes of the immune system. Returning to the previously discussed mastectomized cow study (Kimura et al., 1999), one of the key variables that was different between mastectomized and intact cows was plasma calcium concentration. This revelation rekindled interest in the potential role for calcium metabolism to be causal toward impaired immunity. Kimura et al. (2006) reported that calcium stores in mononuclear leukocytes are depleted prior to the development of hypocalcemia in the blood, and that this depletion of intracellular calcium does potentially contribute to immunosuppression. Nutritional management of periparturient calcium metabolism may have implications for immune function, not just metabolic health.

At the animal level, body condition score is related to the previously discussed metabolites associated with negative energy balance (i.e., NEFA and BHBA). Recent research suggests that immune function is related to body condition score; specifically, it may be that over-conditioned cows are at greater risk for inflammation and infection. It is still early in this area of research, but we are beginning to “connect the dots” to build the scientific story behind fat cows and immune imbalance. It is well documented that over-conditioned cows are at greater risk for metabolic disorders related to energy metabolism (Grummer, 1993; Rukkwamsuk et al., 1999). Specifically, these animals have greater lipid stores entering the period of negative energy balance, and are therefore more likely to have greater concentrations of nonesterified fatty acids (NEFA) and ketones in circulation, and greater triglyceride accumulation in the liver. Each of these factors has been associated with impaired immune function (NEFA – Scalia et al., 2006; Hammon et al., 2006; ketones – Suriyasathaporn et al., 2000; hepatic lipidosis – Andersen et al., 1996). In addition to the energetic related variables, over-conditioned cows are also more likely to experience higher levels of oxidative stress (Bernabucci et al., 2005; O’Boyle et al., 2006), are considered to be at greater inflammatory risk (O’Boyle et al., 2006), and have been reported to have impaired immune function (Lacetera et al., 2005). Greater oxidative stress may impair leukocyte function and also increase the potential inflammatory damage to productive tissue during an immune

response. Insufficient data exists for in-depth discussion of the immune status of severely under-conditioned cattle, but one would expect immunosuppression similar to other examples of malnutrition below some threshold of animal well-being.

The Role of some Dietary Nutrients in Immunity

Completing the relationship between immune function and metabolism, it has also been reported that multiple dietary nutrients influence immunity. The role of dietary nutrients in supporting immune function has received significant research attention. Vitamins (e.g., vitamins C, D, and E) and trace minerals (e.g., zinc or selenium) are all familiar to us from advertisements touting the role of these nutrients in human health and disease. Furthermore, at least basal levels, and in some cases supranutritional levels, of these nutrients have been shown to be supportive for animal health in livestock production systems (Spears and Weiss, 2008; Spears, 2000; Weiss, 1998). Other nutrients such as specific fatty acids have been studied for their ability to influence immune function (Calder, 2006) and hold promise for future use in livestock species.

Although some micronutrients are directly involved in immune cell function, one of the most common ways that nutrients are involved in animal health is through their role as antioxidants. Antioxidants protect the animal from reactive or unstable compounds that set off chain reactions and cause tissue damage. These chain reactions are initiated by oxidized products of metabolism such as superoxide anion, hydrogen peroxide, hydroxyl radical, hypochlorous acid, and peroxynitrite (Valko et al., 2007). These unstable compounds typically fall under the categories of reactive oxygen species (ROS) or reactive nitrogen species (RNS). The ROS and RNS are normal products of healthy metabolism. That is, as energy is created through aerobic metabolism, some unpaired electrons attach to molecular oxygen and form superoxide anion (Valko et al., 2007). This unstable molecule can pass the single electron to other metabolic intermediates or induce instability in other compounds. This group of unstable compounds interacts with lipids, proteins, DNA, and other molecules within the body to induce instability and create tissue damage. The antioxidants that work to oppose these unstable molecules either directly quench these oxidants or sometimes repair tissue that has already suffered oxidative damage. Under basal conditions (in a micronutrient-supplemented animal), antioxidants generally reduce most of the oxidants, and little tissue damage occurs. However, any factor that tips the balance toward greater production of pro-oxidant molecules (e.g., increased metabolic rate, toxins, or inflammation) or decreased presence of antioxidants (e.g., nutrient deficiencies or a greater oxidative stress load) result in greater oxidative stress on the tissues of the animal (Miller et al., 1993).

Oxidative Stress – A Common Denominator between active Metabolism and Inflammation

During inflammatory disease states, immune cells produce ROS and RNS (Sordillo and Aitken, 2009). The leukocytes then use these toxic compounds as part of their arsenal to kill invading pathogens. Indeed, these same molecules that can induce

damage in mammalian tissue can also cause lethal damage to bacteria and other invading pathogens. Although very effective against pathogens, unfortunately these oxidants are not selective about which cells are destroyed and often, significant collateral damage to mammalian tissue occurs. Enter the antioxidants. As previously discussed, antioxidants either present in circulation or residing in tissues, help to preserve the integrity and functionality of the mammalian tissue. If antioxidant status is adequate and the inflammation is moderate, little significant or permanent tissue damage is done. However, severe inflammation or marginal antioxidant protection can lead to extensive tissue damage and permanently compromised tissue function (Zhao and Lacasse, 2008).

Antioxidants typically fall into two groups - either individual nutrients (or compounds) serve to directly quench oxidants, or enzymes containing a specific nutrient at their catalytic site serve to convert these toxic compounds to less harmful intermediates or inert end-products (Miller et al., 1993; Sordillo and Aitken, 2009). Several micronutrients commonly supplemented to livestock serve directly as antioxidants. Tocopherols (vitamin E metabolites) and carotenoids (vitamin A precursors and metabolites) are commonly supplemented to dairy cows commercially, and compounds such as vitamin C, lipoic acid, and glutathione, while not routinely supplemented in commercial diets, are important molecules in oxidative scavenging within the animal. Other nutrients serve as antioxidants within the structure of an enzyme. Of these, selenium is perhaps the most well-studied and recognized as important by commercial nutritionists and veterinarians. Selenium is genetically incorporated into the amino acid selenocysteine and sits at the catalytic site of enzymes such as glutathione peroxidase and thioredoxin reductase, among others (Sordillo and Aitken, 2009). Other micronutrients with important enzymatic antioxidant roles include zinc, copper, manganese, and iron. Although when incorporated into an enzyme, iron has some antioxidant activity, it is most commonly recognized to actually contribute to oxidative stress rather than alleviate it.

Conclusion

Cows experience immune dysfunction around the time of calving. To date, no single factor has been reported to be responsible for this immune dysfunction. Metabolites associated with negative energy balance, such as NEFA and ketones, have been reported to negatively impact immune function. Defective calcium metabolism may also contribute to periparturient immunosuppression. At this time, some of the best strategies for us to avoid losses due to infectious disease are to pay strict attention to the details of close-up and fresh cow management such that metabolic insults to the immune system are avoided. Further research elucidating endocrine, metabolic, and immune interactions around the time of calving are warranted. In addition to metabolites, many dietary nutrients are involved in immune protection and may play roles in immunosuppression. Some of these nutrients are involved in immune cell function, but many others serve to minimize damage to nearby healthy cells during the immune response by limiting inflammatory damage. Much of the potential damage caused during inflammation is due to oxidative stress – the reaction of unstable

oxidizing molecules with tissue lipids, proteins and DNA. Many of the micronutrients that are important for immune function and health serve in this role of tissue protection as antioxidants. Although many of these nutrients are known to be important for health, the quantity of these dietary micronutrients needed to maximize immune function and tissue protection is unknown. Careful nutritional management to provide highly bioavailable nutritional profiles and to maximize metabolic health is currently our best strategy to maximize immune function. In addition to sound nutritional management, best management practices to maximize hygiene and minimize stressors are crucial to helping prevent infection.

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SESSION NOTES