

Inflammation and Nutrient Metabolism in Ruminants

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Introduction

Bovine respiratory disease (**BRD**) causes major physiological and metabolic changes to occur within the immune system and host animal during infection. These changes are caused by infection with both viral and bacterial pathogens, along with the stress of transportation and commingling of calves from multiple sources. The response of the immune system to infection causes changes in blood metabolites such as proteins, cytokines, and other small metabolites. In general, nutrient use is shifted away from accretion in muscle and fat towards synthesis of molecules needed to mount the immune response. These metabolites have the potential to be used as indicators of BRD infection and its consequences on animal growth.

Bovine Respiratory Disease

Bovine respiratory disease is the major cause of morbidity and mortality in feedlot cattle, resulting from the combination of pathogen exposure and stress. Bovine respiratory disease is most common in newly received feedlot cattle that are highly stressed due to transport and commingling, and are being exposed to a host of new pathogens, both viral and bacterial. Bovine respiratory disease can be caused, or at least affected by both preweaning and postweaning factors (Duff and Galvayan, 2007). Proper early nutrition, temperament, and health management (i.e., vaccines) preweaning can help to deter the development of BRD further down the production line. Postweaning factors, such as transportation stress, commingling, nutrition, and management techniques such as castration can also affect the development of BRD (Duff and Galvayan, 2007). Although good management can decrease the risk of BRD development, the combination of unavoidable stress and pathogen exposure can be too much for the calf's host defenses to overcome.

As indicated, pathogens responsible for BRD infection include both viruses and bacteria. Common viral pathogens include bovine viral diarrhea virus (**BVDV**), bovine herpes virus-1 (**BHV-1**), bovine respiratory syncytial virus (**BRSV**) and bovine coronavirus (**BCV**). Although some of these pathogens, such as BVDV, may not initially appear to have direct effects on the respiratory system, they cause respiratory problems

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by affecting the whole body's immune status (Ellis, 2001). The decline in immune status then allows bacterial infections to gain hold in the respiratory tract. Bovine viral diarrhea virus has gained much attention mainly due to its prevalence. Vaccines have been developed for most strains of BVDV; however, even vaccinated calves face some risk of infection because of the multiple strains of BVDV. More than one virus is usually isolated from cattle diagnosed with BRD, once again indicating the complexity of the disease (Duff and Galvayan, 2007).

Bacterial pathogens usually include a combination of *Mannheimia (Pasteurella) haemolytica*, *Pasteurella multocida*, and *Histophilus somni (Haemophilus somnus)* (Ellis, 2001; Apley, 2006). These gram negative bacteria all produce lipopolysaccharides (LPS) and/or lipooligosaccharides as pathogenic factors (Corbeil, 2007; Dabo et al., 2007; Rice et al., 2007). Of the major bacterial pathogens, *M. haemolytica* is generally considered to be the most prevalent and pathogenic. Interestingly, *M. haemolytica* is naturally found in the upper respiratory tract as a native bacterium, but acts as an opportunistic pathogen. It does not become pathogenic unless the immune system becomes compromised, such as during times of stress or infection. *M. haemolytica* produces not only a lipopolysaccharide virulence factor, but also a ruminant specific leukotoxin that targets ruminant leukocytes, which greatly enhances its virulence (Zecchinon et al., 2005).

Another less known bacterial pathogen is *Mycoplasma bovis*. This mycoplasma has recently become the subject of increased research especially in North America. In recent histopathological evaluations of cattle diagnosed with BRD in Canadian feedlots, *M. bovis* was second only to *M. haemolytica* in prevalence, and actually was identified more often than *M. haemolytica* in cattle who were classified as chronically infected by BRD (Booker et al., 2008).

Proteins and Metabolites

The effects of BRD are not just on the respiratory tract – rather, the disease affects whole-body energy and nitrogen metabolism by activating the immune response. Most research on metabolite changes from BRD has focused on the acute phase proteins, such as serum amyloid A (**SAA**), fibrinogen, and most commonly haptoglobin. Focus has also been put on characterizing the entire acute phase response, which includes not only the acute phase proteins, but inflammatory cytokine production as well (Baumann and Gauldie, 1994). Research has been limited on the effects of BRD infection on other non-protein, non-immune response-related metabolites, such as amino acids and monosaccharides. Experiments that have examined the effects of BRD include both controlled infections, where pathogens are known, as well as natural feedlot infection scenarios (Gershwin et al., 2005; Buckham-Sporer et al., 2008; Burciaga-Robles et al., 2010). The detection of a biomarker in serum that is indicative of BRD infection might greatly aid in BRD diagnosis and treatment.

Acute Phase Response

The acute phase response is a non-specific inflammatory reaction to an infection or injury. It is initiated at the site of infection, usually by tissue macrophages or blood monocytes. These immune cells then stimulate the release of cytokines, which initiate a signal cascade that causes the production of cortisol via the adrenal-pituitary axis, which, in concert with other cytokines, eventually results in the production of the acute phase proteins (e.g., SAA, fibrinogen, and haptoglobin) being produced and released by the liver. The acute phase response has been shown to be triggered not only by infection, but also by stress. The acute phase response serves as an important regulator of the defense response, initiating fever, metabolic changes, production of immune cells, and host defense activation which will eventually result in the destruction of pathogens (Baumann and Gauldie, 1994).

Cattle infected with BRD usually have increased concentrations of SAA. In calves that were challenged with BVDV, *M. haemolytica* (MH), or a combination of the two, all groups of infected calves showed increased SAA levels after infection (Gånheim et al., 2003). Calves challenged with the MH infection alone reached maximum SAA concentrations at 1-2 days post infection, while BVDV-challenged calves reached a maximum at 8-9 days after infection. Interestingly, calves which received both BVDV and MH infection exhibited a biphasic response, with 2-3 days between peaks. Calves infected with BVDV/MH also had the most days with higher than baseline levels of SAA (Gånheim et al., 2003).

Increases in SAA levels were also seen in other models of BRD (Heegaard et al., 2000; Carroll et al., 2009). In a trial where calves were infected with BRSV, SAA levels were elevated in all but one of the infected treatment group calves. The SAA levels of BRSV-infected calves reached a peak of 5-7 times greater than control calves between days 5-8 post infection (Heegaard et al., 2000). Cattle injected with a dose of LPS; which can be used as a model of bacterial infection) also showed increases in SAA levels after infection as soon as 7 hours after initial dosing (Carroll et al., 2009). These results indicate that bacterial infections, or intravenous doses of LPS, initiate the acute phase response much quicker than viral infections. Bacterial infections cause an increase in SAA levels within 36 hours after infection, whereas viruses can take up to 9 days after infection for SAA levels to peak.

Fibrinogen levels, like SAA, also increase after infection with BRD pathogens. Calves infected with a viral pathogen (BVDV) had increased fibrinogen levels compared to control calves, with maximum levels reached at 8-9 days after viral inoculation (Gånheim et al., 2003). Comparatively, calves that received just a *M. haemolytica* inoculation showed increased fibrinogen levels within 24 hours post infection. When cattle were first dosed with a virus and then 5 days later given a *M. haemolytica* inoculation, fibrinogen levels did not increase in the 5 days between the inoculations, but reached a maximum 3-5 days after *M. haemolytica* inoculation. The viral-bacterial pathogen calves had a greater overall number of days with elevated (as compared to normal control values) fibrinogen levels than calves with only a viral infection (Gånheim

et al., 2003). These results indicate that like SAA levels, fibrinogen levels increase more rapidly in cattle with bacterial infections than those infected with viruses.

Berry et al. (2004) showed that feedlot cattle treated multiple times for BRD had greater fibrinogen levels than cattle never treated or treated only once. Different pathogens appear to affect levels of fibrinogen. Nikunen et al. (2007) isolated pathogens from cattle naturally infected with BRD, and observed that only cattle from which *P. multocida* was isolated had increased fibrinogen.

Haptoglobin has received the most attention of the three major acute phase proteins. Haptoglobin, like SAA and fibrinogen, increases in serum concentrations after infection. Haptoglobin has been shown to increase following a bacterial challenge with *M. haemolytica*; however, a solely viral infection with BHV-1 did not trigger an increase (Godson et al., 1996). Additionally, increases in haptoglobin were seen in cattle intravenously injected with LPS from *Escherichia coli*, another gram negative bacterium (Jacobsen et al., 2004). Like SAA and fibrinogen, in cattle infected with just *M. haemolytica*, haptoglobin levels peaked at around 2 days post infection, while haptoglobin levels in virally infected cattle (BVDV) did not reach peak haptoglobin levels until day 9 post infection (Gånheim et al., 2003).

In an experiment where cattle were infected dually with BHV-1 and *M. haemolytica*, haptoglobin levels also increased post infection (Aich et al., 2009). The haptoglobin levels were elevated in both cattle that eventually survived infection and those that died (Aich et al., 2009). Haptoglobin levels were also elevated in cattle that were infected with BRSV (Grell et al., 2005). Multiple studies have reported that while elevated levels of haptoglobin were seen in cattle that were treated for BRD in a commercial setting (Berry et al., 2004; Burciaga-Robles et al., 2009), haptoglobin levels were not useful for predicting the number of treatments per animal that would be required (Burciaga-Robles et al., 2009).

The activation of the acute phase response and the subsequent release of acute phase proteins into the serum is a result of infection with BRD pathogens. Similar to cattle, Klasing and Barnes (1998) suggested a switch in amino acid utilization from growth to production of acute phase proteins occurs following an immune challenge in chicks. The synthesis of acute proteins by the liver in response to an immune challenge could change the amino acid requirements as well as energy required for maintenance in support of the acute phase response.

Cytokines

Obviously, any infection or injury to the body will cause the activation of the acute phase response, which involves important molecules besides the acute phase proteins. Cytokines have been shown to increase with infection, although the exact cytokines differ depending on the nature of the infection (viral, bacterial, etc.). Cytokines are small molecules released by immune cells in response to various stimuli, including inflammation and stress, and signal physiological changes. The release of some

cytokines is considered part of the activation of the acute phase response (Baumann and Gaudie, 1994). Accordingly, increases in cytokine concentrations have been shown to occur in BRD challenged cattle. Burciaga-Robles et al. (2010) reported that cattle infected with *M. haemolytica* had increased levels of tumor necrosis factor alpha (TNF- α), interleukin 1-beta (IL-1 β), and interferon- γ (IFN- γ). Similarly, after intravenous dosing with LPS, blood concentrations of TNF- α , interleukin-6 (IL-6), IL-1 β , and IFN- γ were elevated (Carroll et al, 2009).

Virally-infected cattle have slightly altered cytokine expression in comparison to solely bacterial infections. BRSV infected cattle had increases in IL-6 and IFN- γ (Grell et al., 2005), while cattle infected with BVDV had a cytokine profile with heightened levels of TNF- α , IL-1 β , as well as IL-6. Interestingly, cattle that were infected with both BVDV and MH had increases in TNF- α , IL-6, IFN- γ , but not IL-1 β , even though IL-1 β concentrations were high in separate viral and bacterial infections (Burciaga-Robles et al., 2010).

The function of each of these cytokines is well established. IL-1 β , TNF- α , and IL-6 are activated in the first response line of an immune challenge, and their release increases inflammation and acts on the liver to induce the acute phase response. IFN- γ 's major function is the activation of macrophages, which can also be responsible for inflammation (Kindt et al., 2007). Elevated cytokine levels are a good indication of infection, and may serve a role as indicators of disease. However, because of the differences of cytokine profiles between pathogens, as well as a lack of specificity for respiratory disease, other options for BRD biomarkers need to be explored.

Energy Metabolism

There have been few studies that have examined the effects of infection on small, non-mineral, non-protein plasma metabolites. Montgomery et al. (2009) examined how plasma metabolites in heifers upon receiving changed depending on the number of treatments for apparent BRD. These heifers had decreased glucose levels, which could be the result of a hypoglycemic effect due to disease challenge, and/or decreased feed intake due to depression (Montgomery et al., 2009). Conversely, glucose levels increased when cattle were infected with BHV-1 and *M. haemolytica* (Aich et al., 2009). These differences may be due to differences in pathogen load, as well as diet and relation of feeding time to sampling. Lactate levels were also decreased in cattle treated for BRD (Montgomery et al., 2009).

Lactate has been discussed as a possible BRD biomarker. Montgomery et al. (2009) observed a decline in lactate levels as number of BRD treatments increased. The decrease in lactate levels with the number of BRD treatments seen in the Montgomery et al. (2009) experiment is in opposition with Coghe et al. (2000), where BRD infected calves had increased levels of lactate as severity increased. In this trial, high lactate levels were also correlated with increased mortality (Coghe et al., 2000). One explanation for the variability in lactate levels is that the cattle in the Montgomery et al. (2009) experiment may not have had severe enough disease to see an increase in

lactate. The oxygen transport chain has enough backup steps to continue to provide oxygen to tissues unless disease problems become severe (Coghe et al., 2000). Lactate has also been indicated as a biomarker for the prediction of viral-bacterial infection – lactate levels were higher in cattle that died of a combination BHV-1 and *M. haemolytica* infection than those that survived (Aich et al., 2009).

Protein Metabolism

Protein metabolism is affected by disease. For example, cattle that were injected with a dose of LPS, showed decreases in plasma levels of methionine, threonine, leucine, isoleucine, phenylalanine, tryptophan, glycine, serine, asparagine, and tyrosine, while alanine increased (Waggoner et al., 2009b). In a similar experiment, decreases were seen in threonine, lysine, leucine, phenylalanine, tryptophan, asparagine, ornithine, and glutamate, although alanine again increased (Waggoner et al., 2009a). Increased valine was also interpreted as a possible biomarker of concurrent BHV-1 and *M. haemolytica* infection (Aich et al., 2009).

In general, the activation of the immune system during an infection causes a decrease in most plasma amino acid levels. This is due to the increased need for production of immune system cells, such as leukocytes, which can require high levels of specific amino acids (Colditz, 2002). Additionally, the activation of the acute phase response and the subsequent production of acute phase proteins also heighten the need for amino acids and may reduce available plasma amino acid levels (Sandberg et al., 2007). Amino acids are often transported from the muscle to the liver for this specific purpose. Degradation of these amino acids from muscle can also be induced by disease, and not only are these amino acids used for production of proteins or immune cells, they can also be excreted, resulting in further nitrogen loss and muscle wasting (Powanda and Beisel, 2003). Also, as reduced intake is considered a clinical sign of disease (Duff and Galyean, 2007), less protein intake via feedstuffs exacerbates the effects of increased nitrogen usage by the body in order to mount an immune response. In order to meet the demands of the acute phase response and immune system, specific amino acid requirements may increase. Unless amino acids are supplemented into the diet, which is an obvious challenge for ruminant diets, muscle protein will be catabolized to synthesize plasma proteins (Obled, 2003).

Conversely to the results above, amino acid levels were shown to be elevated after BHV-1 infection (Aich et al., 2007). It is possible that different disease factors, such as viral versus bacterial, can affect nitrogen metabolism differently. Increased total plasma N concentrations have also been shown to be greater in cattle treated for BRD than in those that were not (Montgomery et al., 2009). Cattle challenged with IBRV had an increase in total plasma proteins and increased serum N, while excretion of N increased, indicating that disease challenge increased N turnover and affected how N was utilized by tissue (Orr et al, 1988). Overall plasma nitrogen and protein increases are most likely due to the proliferation of the acute phase proteins and immune cells and molecules.

The variability of the effects of BRD on amino acid and protein metabolism may be due to the exact disease model used. LPS injections, which are a model of bacterial infections, tend to decrease amino acid concentrations, whereas viral infections have shown to cause an increase in serum amino acids. The variability of pathogens that can cause BRD also convolutes how BRD affects metabolism, and thus makes the search for a biomarker of BRD more challenging. There are, however, emerging technologies that may hold the key to identifying BRD biomarkers.

Summary

Bovine respiratory disease is the leading cause of morbidity and mortality in North American feedlots, and affects a multitude of biological systems within the animal, including immune activation and energy/protein metabolism. The biological changes that occur with disease status, while not beneficial to the animal, may prove to be useful for identifying infected animals before the presentation of clinical signs. As has been shown in human diseases and model organisms, disease status can be differentiated and biomarkers identified using metabolomic techniques. When applied to BRD, metabolomics could allow for the discovery of early biomarkers of infection in high risk cattle, and lead to improved diagnosis and management.

In the absence of stress or infections, animals will assimilate nutrients into tissues according to their genetic potential and according to age and stage of production. However, during infection, there is an increase in protein turnover due to anorexia induced by cytokine production in response to the pathogen, increased amino acid requirements for acute phase protein synthesis by the liver, and increased mobilization of protein stores from muscle either by decreased synthesis or increased catabolism providing energy precursors for gluconeogenesis or amino acids for protein synthesis by the liver.

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SESSION NOTES