Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA)
Available online at www.inia.es/sjar

Spanish Journal of Agricultural Research 2011 9(2), 414-422
ISSN: 1695-971-X
eISSN: 2171-9292

Physiological, biochemical and histopathological effects of fermentative acidosis in ruminant production: a minimal review

Y. Xu and Z. Ding*

Faculty of Animal Sciences and Technology. Guangxi University. 530005 Nanning (Guangxi). China

Abstract

Rumen acidosis is increasingly recognized as a significant disorder in ruminants that increases the morbidity and mortality of animals, especially for dairy cattle and sheep. Acidosis is not just D-lactate which disturbs the acid-base status and the severity of acidosis is related to many factors and not only due to the level of lactic acid production, resulting in difficulties in diagnosing acidosis. Therefore, an understanding of the physiological, biochemical, and histopathological effects of rumen acidosis is fundamental for developing effective methods of prevention and treatment of fermentative acidosis. The present review evaluates the physiology, biochemistry, and pathophysiology of fermentative acidosis as well as gives a conclusion and look-forward. The information will benefit the health and welfare of ruminants and contribute to modern systems of ruminant production.

Additional key words: acid accumulation; diagnosis; influence; livestock.

Resumen

Efectos fisiológicos, bioquímicos e histopatológicos de la acidosis fermentativa en la producción de rumiantes: una mini-revisión

Cada vez está más reconocido que la acidosis ruminal es un trastorno importante de los rumiantes que aumenta la morbilidad y la mortalidad de los animales, especialmente de vacas lecheras y ovejas. La acidosis no es sólo D-lactato, que perturba el estado ácido-base; la gravedad de la acidosis se relaciona con muchos factores y no sólo con el nivel de producción de ácido láctico, lo que presenta dificultades para el diagnóstico de la acidosis. Por lo tanto, para el desarrollo de métodos eficaces de prevención y tratamiento de la acidosis fermentativa, es fundamental una comprensión de los efectos fisiológicos, bioquímicos e histopatológicos de la acidosis ruminal. La presente revisión evalúa y presenta conclusiones de la fisiología, bioquímica y fisiopatología de la acidosis fermentativa. Esta información será beneficiosa para la salud y el bienestar de los rumiantes y contribuirá a los sistemas actuales de producción de rumiantes.

Palabras clave adicionales: acumulación de ácidos; diagnóstico; ganadería; influencia.

Introduction

When the ruminant ingests abruptly large amounts of readily fermentable carbohydrates (RFCs) or when the period of adaptation to RFCs is insufficient, RFCs are suddenly fermentated and volatile fatty acids (VFAs) are accumulated, resulting in the rumen pH to drop below 5.5 for a prolonged period and creating the condition of fermentative acidosis (Ding *et al.*, 1996, 1997, 1998; Ding and Xu, 2003). In this condition, lactic acid-producing bacteria, such as *Streptococcus bovis* and *Lactobacillus* spp., are proliferated, leading to the accumulation of lactic acid, which is known as lactic acidosis (Gozho *et al.*, 2005, 2006, 2007).

Although acidosis has drawn researchers' attention for a long time, it remains a major health threat in ruminants. Krause and Oetzel (2006) pointed out that acidosis is still a major problem for the North American dairy industry and subacute ruminal acidosis (SARA) is increasingly recognized as a significant disorder in

* Corresponding author: zhaokund@hotmail.com
Received: 23-05-10; Accepted:29-03-11.

Abbreviations used: AGS (acidic gut syndrome), DMI (dry matter intake), FCs (readily fermentable carbohydrates), GGTP (gamma glutamine trans-peptidase), LPS (lipopolysaccaride endotoxin), SARA (subacute ruminal acidosis), VFAs (volatile fatty acids).

ruminants. SARA and associated lameness both appear to be very prevalent problems throughout the US dairy industry (Stone, 2004). This condition increases the morbidity and mortality of stock, as well as markedly reduces weight gain in feedlot sheep and cattle. It may be the most significant health disorder in ruminants fed on high-quality pastures and grain (RAGFAR, 2007). SARA costs the North American dairy industry between 500 million and 1 billion annually (Enemark, 2009).

It is generally believed that fermentative acidosis is caused by the intake of great amounts of RFCs and is thus a management problem. However, fermentative acidosis depends on a number of factors, including the amount of RFCs consumed, rates of production and absorption of acids (lactic acid, VFAs and other acids), buffering capacity, and so on (Ding and Xu, 2006; Xu and Ding, 2006). The pathogeny and diagnosis could be more complex. However, so far only limited information on the pathogeny of the disease is available for diagnosing SARA (Bevans *et al.*, 2005; Xu and Ding, 2006; Plaizier *et al.*, 2008).

The objective of this review is to evaluate the extant research in physiology, biochemistry, and histopathology of fermentative acidosis in ruminants, with particular attention in sheep and dairy cattle. The information will contribute to the diagnosis, prevention, and treatment of acidosis in ruminants.

Acidosis and its primary causes

Usually, rumen pH tends to be relatively constant (normally at pH 7.5 or a bit lower), depending on what the animal eats and the time of the day. A relatively constant level of rumen pH is very important to maintain normal functioning of the rumen. The maintenance of the rumen pH at a relatively constant level depends on the balance between rates of acid production and absorption and the buffering capacity of the animal. Buffering capacity provided by buffers in the rumen and salivary glands plays a key role (Ding *et al.*, 1996, 1997), though the respiratory and excretory systems also function in pH regulation via blood; for example, carbon dioxide (CO_2) is exhaled from the lung and excess H^+, NH_3, and K^+ are excreted in the urine (Rawn, 1989).

Normally, the production and excretion of acids are balanced to maintain systemic acid-base homeostasis. Ruminants are generally able to maintain ruminal pH levels within physiological limits through their own regulation of intake, endogenous buffer production, microbial adaptation, and VFA absorption (Krause and Oetzel, 2006; Bramley *et al.,* 2008).

However, systemic acid-base homeostasis may be occasionally broken. For example, if the ruminant abruptly ingests large amounts of grain, starch or other feed that is rich in RFCs, much lactic acid will be formed and this is associated with a fall in pH in the rumen leading to fermentative acidosis, therefore, it is also known as ruminal acidosis (Nocek, 1997; Krause and Oetzel, 2006). Fermentative acidosis is considered to be due to faster and complete fermentation of RFCs in the rumen. Lactic acid accumulates only if its rate of production exceeds the rate of utilization or conversion to VFAs. This can result from either a proliferation of lactate producers (Gram-positive bacteria) or a failure of lactate utilizers (Gram-negative bacteria) to proliferate rapidly enough to utilize the increased quantity of the acid, which occurs when there is an accumulation of VFAs and a reduced pH (Rowe *et al.*, 1989). A low level of ruminal pH reduces the number of species of bacteria in the rumen during SARA, although the metabolic activity of the bacteria remains very high (Garry, 2002).

An extensive range of carbohydrates has been reported to produce lactic acid either *in vivo* or *in vitro*. Any feedstuff rich in soluble carbohydrates is capable of acting as a lactic acid precursor. In times of drought, there can be significant risk of acidosis for ruminants, where the animals are often given access to grain stubble after harvest. These ruminants usually do not go through any adaptation stage. A similar situation can occur when ruminants are introduced into crops, particularly brassicas, such as rapes (*Brassica chinensis* L.), kales (*Brassica oleracea* var. *acephala f. tricolor*) or turnips (*Brassica rapa* var. *rapa*), that are highly digestible; and also when ruminants selectively graze the most digestible material (RAGFAR, 2007; Walsha *et al.,* 2009).

A rank order of grains and by-product feeds in terms of their lactic acid production potentials, based on results of fermentation and in the order of the greatest to the least potential to produce lactic acid, showed that steam-flaked barley = barley = wheat > citrus pulp > beet pulp = corn > high moisture corn = sorghum grain (Cullen *et al.*, 1986). Furthermore, steam flaking, rolling, popping or other processing methods increase the surface area or gelatinized starch and make carbohydrates more rapidly fermentable, thereby increasing the potential for fermentative acidosis (Huntington, 1988).

Acidosis is a condition with severe consequences for the animal. The clinical signs of acidosis vary depending on the severity of the disease (Braun *et al.*, 1992) and can be either acute, posing a life-threatening situation, or subacute (chronic), resulting in reduced feed consumption and weight gain. Repeated bouts of SARA can damage the surface of the rumen wall (Krause and Oetzel, 2006). Once the rumen wall is damaged, bacteria and toxins produced by bacteria can enter the portal circulation, causing liver abscesses and an inflammatory response (Gozho *et al.*, 2005, 2006, 2007). Clinical signs of acidosis in sheep are similar to those in cattle. Sheep differ from cattle in rumen function and feed tends to pass quicker through the rumen than in cattle. Sheep tend to have a higher incidence of intestinal disturbances compared to cattle, *e.g.* enterotoxaemia (Pulina, 2004).

The adverse effects of acidosis are attributed to the local effects of pH and excess lactic acid in the rumen (Juhász and Szegedi, 1968) because both D- and L-lactic acid are absorbed across the rumen wall and depress blood pH. This effect was also thought to be exacerbated by the slower clearance by the body of D-lactic acid originated from digestive microbes and is thus referred to as "D-lactic acidosis" (Blood and Henderson, 1963). However, the concentrations of D-lactate in blood during episodes of rumen lactic acidosis are normally very much lower than that of L-lactate (Godfrey *et al.*, 1992). It is possible that L-lactic acid predominates in the fermentative production (Ryan, 1964) or both D- and L-lactic acid are produced in approximately equal amounts by digestive microbes (Cori and Cori, 1929). On the other hand, only L-lactate is produced by metabolism of animal tissues and the conversion from propionate by the epithelium of digestive tract (Giesecke and Stangassinger, 1980). Therefore, the concentration of L-lactic acid is usually higher than that of D-lactic acid (Ganter *et al.*, 1993). Cori and Cori (1929) and Dunlop and Hammond (1965) found that there was no detectable difference in the absorption rate between the two isomers and suggested that the peak of L- and D-lactic acid into the blood should occur at the same time. However, liver tissue was found to be able to synthesize carbohydrate from D-lactic acid but scarcely any from L-lactic acid (Meyerhof and Lohmann, 1926). L-lactic acid is utilized 4 times more slowly in the rat than D-lactic acid because D-lactic acid can be deposited as liver glycogen (Cori and Cori, 1929).

The severity of acidosis is related to many factors and not only lactic acid production (Lindinger and Heigenhauser, 2008). It is important to emphasize the contribution of all acids to the disruption of the acid-base status during acidosis (Harmon, 1983). Rowe (1997) suggested that a new condition, "acidic gut syndrome" (AGS), should be recognized. This is characterized by the accumulation of acids in the digestive tract at concentrations that have not previously been considered harmful to animals or humans. The detrimental effects initiated by lactic acid and low pH may be mediated through direct action on the gut wall, through the production of bacterial endotoxin, through the combination of acids and endotoxins, or through other factors.

Adverse effects of acidosis include physiological, biochemical, and histopathological aspects which are discussed below.

Physiological effects of acidosis on the animal

A series of physiological effects may happen in acidotic animals and the effects may relate to many factors.

Decreased dry matter intake (DMI) is an obvious cause for acidosis and has been used as a clinical sign to diagnose SARA (Kleen *et al.*, 2003; Oetzel, 2003). A lowered feed intake was observed during periods of SARA (Olsson *et al.*, 1998; Brown *et al.*, 2000; Krajcarski-Hunt *et al.*, 2002; Gozho *et al.*, 2005, 2006; Fairfield *et al.*, 2007). Reasons for the feed intake depression can include reduced fiber digestibility (Plaizier *et al.*, 2001; Krajcarski-Hunt *et al.*, 2002) and increases in VFAs, especially propionate, and in the osmolarity in the rumen (Allen, 2000; Gozho *et al.*, 2006; Khafipoor *et al.*, 2006, 2007; Enemark, 2009). Inflammation of the ruminal epithelium (rumenitis) could also play a role in depressing feed intake following ruminal acidosis (Krause and Oetzel, 2006). Rumenitis was caused by grain-induced SARA (Gozho *et al.*, 2005, 2006, 2007) and reduced feed intake in the cow (Weingarten, 1996; Andersen, 2000).

The severity of rumenitis caused by SARA most likely depends on conditions in the rumen, such as pH, composition of microbial populations, existing challenges to the barrier function, and inflammation of the rumen mucosa. The severity of clinical signs appears to reach a maximum between 12 and 36 hours in sheep (Patra *et al.*, 1995). If clinical signs are more severe, it may transform into acute acidosis.

The reduction in fiber digestion that occurs during SARA is most likely the result of the acid sensitivity

of the fibrolytic rumen bacteria. These bacteria generally cannot tolerate a rumen pH below 6.0, which will reduce their numbers in the rumen and, subsequently, reduce fiber digestion (Shi and Weimer, 2002).

Diarrhea has been associated with SARA in dairy herds by many scientists (Nocek, 1997; Kleen *et al.*, 2003; Oetzel, 2003). Feces from cows with SARA may appear brighter and more yellowish than the feces of cows without SARA (Kleen *et al.*, 2003). This is because fecal consistency is determined by the movement of water into the digestive tract and as a result of SARA, digesta is hypertonic compared to plasma (Huber, 1976). In SARA cases, the faeces appear foamy with gas bubbles, and contain more than normal amounts of undigested fiber or grain (Hall, 2002). Foamy feces and diarrhea suggest extensive hindgut fermentation which has also been associated with SARA (Nordlund *et al.*, 2004). Rumen stasis, as a result of low rumen pH, may also allow for the accumulation of free gas (Rebhun, 1995). However, the blood gas parameters are not notably affected in cases of chronic, metabolic acidosis (Lachmann and Siebert, 1980). Because there is an insufficient ruminal fiber mat, fiber is not effectively retained in the rumen (Hall, 2002). Nordlund *et al.* (1995) reported on herds with soft faeces that contained substantial amounts of undigested feed particles. Intermittent diarrhea and the presence of undigested particles indicate inadequate digestion and fast passage of feed.

Cows affected with SARA may develop caudal vena cava syndrome which is presented clinically as hemoptysis and peracute deaths due to massive pulmonary hemorrhage (Nordlund *et al.*, 1995). In these cases, septic emboli from liver abscesses cause foci of pulmonary infection that ultimately invade pulmonary vessels and cause their rupture (Radostits *et al.*, 1994; Rebhun, 1995). Therefore, SARA is associated with liver abscesses (Dirksen *et al.*, 1985; Nocek, 1997; Kleen *et al.*, 2003; Oetzel, 2003). These liver abscesses are caused by translocation of rumen bacteria, such as *Fusobacterium necrophorum* and *Arcanobacterium pyogenes,* to the portal blood as a result of decreased barrier function of the rumen mucosa (Dirksen *et al.*, 1985; Nocek, 1997; Kleen *et al.*, 2003). These bacteria can spread from the liver to other organs, such as the heart, lungs, and kidneys (Nordlund *et al.*, 1995; Nocek, 1997; Kleen *et al.*, 2003; Oetzel, 2003). The reduced barrier function of the rumen mucosa is associated with rumenitis and lesions in the rumen mucosa due to the low rumen pH that occurs during SARA (Nocek, 1997; Andersen, 2000; Kleen *et al.*, 2003). Rumenitis also leads to a high incidence of liver abscesses (Church, 1993) in feedlot cattle.

If the treatment is not appropriate, acute acidosis can kill ruminants in the short term, and SARA can also kill ruminants through dehydration due to excessive water loss in the faeces (scouring). If animals survive this shock, rumenitis permits microbial contamination of the blood and animals may die after some weeks. Culling rate and number of inexplicable deaths within herds with SARA may be unacceptably high (Nordlund and Garret, 1994).

Biochemical effects of acidosis on the animal

Acidosis can result in a lot of biochemical effects in the ruminant. Rumen pH will fall when organic acids, such as VFAs and lactic acid, accumulate in the rumen, and if rumen buffering cannot keep pace with the accumulation of these acids. Because of rapid fermentation of RFCs in the rumen, increased concentration of lactic acid and VFAs and lowered pH have been reported in the rumen liquor of acidotic sheep (Phillipson and McAnally, 1942), cattle (Balch and Rowland, 1957) and goats (Sen *et al.*, 1982). Many of the mechanisms by which depression of rumen pH compromises cow health are not well understood. Recent research has suggested that the production of immunogens in the rumen, such as lipopolysaccaride endotoxin (LPS) and histamine, reduction of the barrier function of the rumen, and translocation of immunogens from the rumen are part of these mechanisms (Plaizier *et al.*, 2008). Rumen pH depression triggers the release of vasoactive substances, such as histamine and LPS, which damage the capillaries of the lamellae in the foot, thus causing hemorrhage, inflammation, and lameness (Nocek, 1997). On the other hand, grain-induced SARA increased lysis of Gram-negative bacteria, resulting in an increase of acute phase proteins, haptoglobin and serum amyloid-A, in cow plasma and milk, and stimulated translocation of LPS into the blood (Gozho *et al.*, 2005, 2006, 2007). Moreover, Plaizier *et al.* (2008) reported that the reduction of milk fat and milk protein applied to an entire lactation.

Histamine is an important regulator of feed and water intake in cattle (Lecklin and Tuomisto, 1990; Rossi *et al.*, 1998). Recent experiments have demonstrated that the permeability of rumen epithelia to

histamine is low when ruminal pH is normal, but absorption increases significantly when pH declines (Aschenbach *et al.*, 2000). Thus, declining ruminal pH predisposes animals to increased absorption of histamine. Increased sugar levels in blood may be an indication of internal metabolism initiated by acidosis in the rumen and mediated via toxic substances, such as lactate and histamine (Nikolov, 1996). High levels of histamine are involved in the pathogenesis of bronchial constriction (Vignola *et al.*, 1997) and cardiovascular shock (Nakamura *et al.*, 1997).

Prentice (2000) reported a rise in serum haptoglobins (acute-phase inflammatory proteins) and an increase in the prevalence of ruminal biopsy samples with histological evidence of rumenitis when Holstein steers were fed to a low target ruminal pH.

However, Gozho *et al.* (2007) demonstrated that grain-induced SARA increased free LPS in the rumen, but not in peripheral blood, which disagrees with the hypothesis of Nocek (1997) that LPS damages the capillaries of the hoof. Intravenous administration of LPS causes immune activation, including the production of cytokines and increase in acute phase proteins in the peripheral blood (Werling *et al.*, 1996; Waldron *et al.*, 2003). Hence, the inflammation that accompanies grain-induced SARA could be the result of LPS translocation from the rumen to the liver. It is unclear if LPS is responsible for rumenitis, as low rumen pH can also lead to rumenitis (Nocek, 1997; Kleen *et al.*, 2003; Oetzel, 2003). At present, the pathogenesis of rumenitis seems to be mediated by an increased production of VFAs, particularly butyrate and propionate, as well as a temporary rise in the ruminal lactate concentration and fluctuations in the osmolality of the rumen fluid, which may be involved in the development of the rumenitis (Dirksen, 1985; Krehbiel *et al.*, 1995).

The activities of some enzymes change in acidosis because the animal metabolism, environment and pH of the enzymes have changed. Elevated activities of amylase, creatinine phosphokinase and gamma glutamine trans-peptidase (GGTP) were revealed in serum enzyme profiles of acidotic sheep (Patra *et al.*, 1996). The change in serum amylase may be attributed to change in carbohydrate metabolism (Kaneko, 1989) and lowering of rumen pH (Slyter, 1976). Creatinine phosphokinase activity is one of the most specific indicators of muscle damage (Kaneko, 1989) and hence increased activity of this enzyme may be a signal to muscle damage in acidosis. Increased activity of GGTP, a liver-specific enzyme, reflects hepatobiliary damage (Patra *et al.*, 1996).

Grain-induced SARA causes an increase in acute phase proteins in blood, which is an indicator of inflammation. This has been shown by several studies (Gozho *et al.*, 2005, 2006, 2007). Increased concentrations of urea and total protein in the blood have also been observed in experimentally acidotic sheep (Juhász and Szegedi, 1968). Chikagwa-Malunga *et al.* (2009) reported that increasing the supplementary level of *Mucuna* sp. (a leguminous used in animal feeding) with relatively high crude protein increased ($p < 0.05$) level and efficiency of microbial protein synthesis, ruminal fluid acidity, total VFA concentration, decreased ($p < 0.05$) coccidian oocyst scores, and tended ($p < 0.10$) to increase N retention. Rumenitis might initiate the production of certain acute phase proteins which are produced in the liver and then released into blood (Gozho *et al.*, 2005, 2006).

The change of rumen osmolarity can cause serious problems in the acidotic animal. Many of the symptoms, such as diarrhea, haemoconcentration, and pronounced dehydration associated with the grain engorgement syndrome, have been shown to be attributable to an increase in osmotic pressure of the rumen and not due to the absorption of lactic acid or any other toxic factor (Patra *et al.*, 1995). Osmotic pressures in excess of 500 mOsmol L^{-1} were reported in ruminal fluid of a heifer experimentally engorged with wheat (Ahrens, 1967).

Excess CO_2 formed in the rumen during fermentation in the pathological process also exacerbates the symptoms through paralyzing the respiratory centre, a relative oxygen deficiency (hypoxia) and absolute accumulation of CO_2 in the tissue so that the affected animals die of asphyxia (Juhász and Szegedi, 1968).

Many other blood components also change in the animal with acidosis. Pyruvic acid, inorganic phosphate, and haematocrit value increased in sheep overloaded with RFCs, whereas blood Na^+ and Cl^- concentration declined (Juhász and Szegedi, 1968). Excessive amounts of excreted phosphate were found in the urine of cows fed high grain diets (Enemark *et al.*, 2004). Serum urea changing is another characteristic in acidotic animals. A significant increase in serum urea is an index of a decreased glomerular filtration rate in acidotic sheep, possibly due to renal damage or reduction in effective renal blood flow, and a fall in the arterial blood pressure, which results in subnormal renal function (Dunlop, 1972).

Histopathological effects of acidosis on the animal

There is a series of histopathological changes in different organs of acidotic ruminants. The rumen shows denudation and broken continuity (Vestweber and Leipold, 1974). There is micro-vesiculation in the stratum lucidum with infiltration of polymorphs in and around vesicles. A few vesicles coalesce to form larger ones. Mucosal papillae reveal infiltration of polymorphs and mononuclear cells. Ruminal papillae shows hydropic degeneration of epithelial cells that start in the deeper layer. With time, micro-vesicles increase in size and move towards the superficial layers with loss of integrity of epithelium in many areas. At the same time, the liver is congested with evidence of hemorrhage in the parenchyma (Patra *et al.*, 1995; Puntenney *et al.,* 2003). Sinusoids are distended with red blood cells. There are peri-portal and peri-vascular mononuclear infiltration, degenerative and focal necrotic changes in hepatocytes (Patra *et al.*, 1995).

Ruminal epithelial cells are not protected by mucus and are vulnerable to the chemical damage by acids. Thus, low ruminal pH can lead to rumenitis (Nocek, 1997; Kleen *et al.*, 2003; Oetzel, 2003) and eventually to ruminal parakeratosis, erosion and ulceration of the ruminal epithelium (Garry, 2002). Rumenitis is the fundamental lesion of SARA and initiates chronic health problems. Once the ruminal epithelium is inflamed, bacteria may colonize the papillae and leak into portal circulation. These bacteria may cause liver abscesses, which sometimes cause peritonitis around the site of the abscess. If the ruminal bacteria clear the liver (or if bacteria from liver infections are released into circulate on), they may colonize the lungs, heart valves, kidneys or joints (Nordlund *et al.*, 1995; Nocek, 1997). The resulting pneumonia, endocarditis, pyelonephritis and arthritis are difficult to diagnose antemortem (Krause and Oetzel, 2006). Parakeratosis may affect VFA absorption in the long term when it occurs as a consequence of acute increased lactate production caused by induced clinical acute rumen acidosis (Krehbiel *et al.*, 1995). Mucosal lesions in rumenitis may serve as an entrance for *Fusobacterium necrophorum*, and, more rarely, *Acanobacterium pyogenes*, with subsequent colonization in the submucosa in severe cases of SARA. Embolic spread to the liver results in hepatic abscess formation (the rumenitis liver abscess complex), occasionally with metastasis to the pulmonary circulation via the posterior vena cava, causing rupture of minor pulmonary arteries into the bronchi (the caudal vena cava syndrome). Clinically, these episodes may lead to epistaxis and/or haemoptysis; characterized by bloody, foaming expectorate around the muzzle and nostrils. Subacute ruminal acidosis may also be associated with sole ulcers (Nocek, 1997). Feed-induced acidosis has been shown to result in abomasal ulceration in goats, however, the pathogenesis is not yet fully understood (Aslan *et al.*, 1995).

SARA may be associated with laminitis and subsequent hoof overgrowth and sole abscesses. Laminitis (pododermatitis aseptica diffusa) is defined as the inflammation of the dermal layers inside the foot and has been associated with systemic metabolic insults (Nocek, 1997). Laminitis generally do not appear until weeks or months after the bout of ruminal acidosis that caused them. The true mechanistic causes of laminitis in dairy cows are assumed to be multi-factorial, the precise mechanism by which SARA increases the risk for laminitis has not been characterized (Nocek, 1997; Ruegg, 2000). Laminitis in horses can be caused by metalloproteinase enzymes that destroy the lamellar detachment (Kyaw-Tanner and Pollitt, 2004). The information from equine studies has shown that an exotoxin released from *S. bovis* may activate metalloproteinase enzymes and lead to the separation of equine lamellar explants (Mungall *et al.*, 2001). These results could indicate a link between damage to the integrity of the hoof and *S. bovis*, which might proliferate during bouts of SARA. This disorder is prevalent in dairy cows during early lactation and in beef cattle in feedlots (Underwood, 1992).

The severity and the signs of acidosis depend on the animal. Rumen acidosis (rumen pH < 5.4) was recorded in some goats exposed to *ad libitum* concentrates in the post-partum period, however, no clinical signs of acidosis or laminitis were observed (Mgasa and Arnbjerg, 1993) because goats can suffer from rumen acidosis without suffering from metabolic acidosis (Giger-Reverdin *et al.*, 2006). This appears to be because adult goats have a stable rumen structure and are resistant to laminitis even when exposed to high amounts of concentrates (Magasa and Arnbjerg, 1993).

Conclusion and look-forward

Summarily, the adverse effects of acidosis in ruminants are complex and a multidisciplinary approach is needed for an understanding, prevention and treatment

of acidosis. Currently, careful management and gradual adaptation to diets high in RFCs are the most important to prevent fermentative acidosis.

Improved diagnostic measures need to be developed and further research is required to define roughage/fiber requirements for feedlot animals. A computer model may have a potential role to predict the profile of nutrients available, lactic acid production and the efficacy of treatment of acidosis. Many genes may participate in various processes leading to the adaptation and restoration of normal systemic acid-base and electrolyte homeostasis. Ruminal acidosis will become an even more common problem as genetic progress and better feeding management allow cows to consume more feed.

Acknowledgements

This work was partly funded through Guangxi Postgraduate Education Innovation Fund (T31049, T31066, 2009105930908M012) and Innovation Fund, Guangxi University (L300261).

References

AHRENS F.A., 1967. Histamine, lactic acid, and hyper tonicity as factors in the development of rumenitis in cattle. Am J Vet Res 28, 1335-1342.

ALLEN M.S., 2000. Effects of diet on short-term regulation of feed intake by lactating dairy cattle. J Dairy Sci 83, 1598-1624.

ANDERSEN P.H., 2000. Bovine endotoxicosis: aspects of relevance to ruminal acidosis. PhD thesis. The Royal Veterinary and Agricultural University, Copenhagen.

ASCHENBACH J.R., OSWALD R., GABEL G., 2000. Transport, catabolism and release of histamine in the ruminal epithelium of sheep. Pflugers Arch 440, 171-178.

ASLAN V., THAMSBORG S.M., JØRGENSEN R.J., BASSE A., 1995. Induced acute ruminal acidosis in goats treated with yeast (*Saccharomyces cerevisiae*) and bicarbonate. Acta Vet Scand 36, 65-77.

BALCH D.A., ROWLAND S.J., 1957. Volatile fatty acids and lactic acid in the rumen of dairy cows receiving a variety of diets. Bri J Nutr 11, 288-298.

BEVANS D.W., BEAUCHEMIN K.A., SCHWARTZKOPF-GENSWEIN K.S., McKINNON J.J., McALLISTER T.A., 2005. Effect of rapid or gradual grain adaptation on subacute acidosis and feed intake by feedlot cattle. J Anim Sci 83, 1116-1132.

BLOOD D.L., HENDERSON J.A., 1963. Veterinary medicine, 3rd ed. Williams and Wilkins Co, Baltimore, MD, USA.

BRAMLEY E., LEAN I.J., FULKERSON W.J., STEVENSON M.A., RABIEE A.R., COSTA N.D., 2008. The definition of acidosis in dairy herds predominantly fed on pasture and concentrates. J Dairy Sci 91, 308-321.

BRAUN U., RIHS T., SCHEFER U., 1992. Ruminal lactic acidosis in sheep and goats. Vet Res 130, 343-349.

BROWN M.S., KREHBIEL C.R., GALYEAN M.L., REMMENGA P., PETERS J.P., HIBBARD B., ROBINSON J., MOSELEY W.M., 2000. Evaluation of models of acute and subacute acidosis on dry matter intake, ruminal fermentation, blood chemistry, and endocrine profiles of beef steers. J Anim Sci 78, 3155-3168.

CHIKAGWA-MALUNGA S.K., ADESOGAN A.T., SZABO N.J., LITTELL R.C., PHATAK S.C., KIM S.C., ARRIOLA K.G., HUISDEN C.M., DEAN D.B., KRUEGER N.A., 2009. Nutritional characterization of *Mucuna pruriens:* 3. Effect of replacing soybean meal with Mucuna on intake, digestibility, N balance and microbial protein synthesis in sheep. Anim Feed Sci Technol 148(2-4), 107-123.

CHURCH D.C., 1993. The ruminant animal, digestive physiology and nutrition. Swaziland Press, Inc Prospect Heights, Illinois, USA.

CORI C.F., CORI G.T., 1929. Glycogen formation in the liver from D- and L-lactic acid. J Biol Chem 81, 389-403.

CULLEN A.J., HARMON D.L., NAGARAJA T.G., 1986. In vitro fermentation of sugars, grain, and by-product feeds in relation to initiation of ruminal lactate production. J Dairy Sci 69, 2616-2621.

DING Z., ROWE J., GODWIN I., XU Y., 1996. Buffering capacities of rumen and caecal digesta from sheep. Aust Anim Prod 21, 343.

DING Z., ROWE J., GODWIN I., XU Y., 1997. The buffering capacity of caecal digesta exceeds that of rumen digesta from sheep fed pasture or roughage diets. Aust J Agr Res 48, 723-728.

DING Z., ROWE J., GODWIN I., XU Y., 1998. No lactic acid absorbed from the caecum and rumen of sheep. Aust J Agr Res 49, 293-301.

DING Z., XU Y., 2003. Lactic acid is absorbed from the small intestine of sheep. J Exp Zool 295A(1), 29-36.

DING Z., XU Y., 2006. A model for exploring lactic acidosis: 1. Model description. Belg J Zool 136(2), 117-124.

DIRKSEN G., 1985. Der Pansenazidose-Kompleks neuere Erkentnisse und Erfahrungen (1). Tierärztliche Praxis 13, 501-512. [In German].

DIRKSEN G.U., LIEBICH H.G., MAYER E., 1985. Adaptive changes of the ruminal mucosa and their functional and clinical significance. Bov Pract 20, 116.

DUNLOP R.H., 1972. Pathogenesis of ruminant lactic acidosis. Adv Vet Sci Comp Med 16, 259-302.

DUNLOP R.H., HAMMOND P.B., 1965. D-lactic acidosis of ruminants. Ann NY Acad Sci 119, 1109-1132.

ENEMARK J.M.D., 2009. The monitoring, prevention and treatment of sub-acute ruminal acidosis (SARA): a review. Vet J 176(1), 32-43.

ENEMARK J.M.D., JØRGENSEN R.J., KRISTENSEN N.B., 2004. An evaluation of parameters for the detection

of subclinical rumen acidosis in dairy herds. Vet Res Commun 28, 687-709.

FAIRFIELD A.M., PLAIZIER J.C., DUFFIELD T.F., LINDINGER M.I., BAGG R., DICK P., MCBRIDE B.W., 2007. Effects of a prepartum administration of a monensin controlled release capsule on rumen pH, feed intake, and milk production of transition dairy cows. J Dairy Sci 90, 937-945.

GANTER M., BICKHARDT K., WINICKER M., SCHWERT B., 1993. Experimental investigations about the pathogenesis of rumen acidosis in sheep. J Vet Med Ser A 40, 731-740.

GARRY F.B., 2002. Indigestion in ruminants. In: Large animal internal medicine (Smith B.P., ed). Mosby-Year Book, Mosby, St Louis, MO, USA. pp. 722-747.

GIESECKE D., STANGASSINGER M., 1980. Lactic acid metabolism. In: digestive physiology and metabolism in ruminants (Ruckebusch Y., Thivend P., eds). MTP Press Ltd, Int Medical Publ, Westport, CT, USA. pp. 523-539.

GIGER-REVERDIN S., DESNOYERS M., DUVAUX-PONTER C., SAUVANT D., 2006. Rumen and metabolic acidosis in dairy goats are independent. J Dairy Sci 89 (Suppl. 1), 215 (Abstr.).

GODFREY S.I., BOYCE M.D., ROWE J.B., SPEIJERS E.J., 1992. Changes within the digestive tract of sheep following engorgement with barley. Aust J Agr Res 44, 1093-1101.

GOZHO G.N., PLAIZIER J.C., KRAUSE D.O., KENNEDY A.D., WITTENBERG K.M., 2005. Subacute ruminal acidosis induces ruminal lipopolysaccharide release and triggers an inflammatory response. J Dairy Sci 88, 1399-1403.

GOZHO G.N., PLAIZIER J.C., KRAUSE D.O., 2006. Effects of grain induced subacute ruminal acidosis on ruminal lipopolysaccharide and inflammation in Holstein cows. J Dairy Sci 89 (Suppl 1), 404.

GOZHO G.N., PLAIZIER J.C., KRAUSE D.O., 2007. Ruminal lipopolysaccharide concentration and inflammatory response during grain induced subacute ruminal acidosis in dairy cows. J Dairy Sci 90, 856-866.

HALL M.B., 2002. Characteristics of manure. Proc Tri-state Dairy Nutrition Conference, April 16-17. Fort Wayne, IN, USA. pp. 141-147.

HARMON D.L., 1983. D(-)lactate metabolism in beef cattle. PhD dissertation. University of Nebraska, Lincoln, NE, USA.

HUBER T.L., 1976. Physiological effects of acidosis on feedlot cattle. J Anim Sci 43, 902-909.

HUNTINGTON G.B., 1988. Acidosis. In: The ruminant animal, digestive physiology and nutrition (Church D.C., ed). Waveland Press, Inc Prospect Heights, IL, USA. pp. 474-480.

JUHÁSZ B., SZEGEDI B., 1968. Pathogenesis of rumen overload in sheep. Acta Vet Acad Sci Hung 18, 63-80.

KANEKO J.J.I., 1989. Clinical biochemistry of domestic animals, 4th ed. Academic Press, NY, USA.

KHAFIPOOR E., KRAUSE D.O., PLAIZIER J.C., 2006. Influence of grain induced sub-acute ruminal acidosis (SARA) on lipopolysaccharide endotoxin (LPS) and acute phase proteins. Can J Anim Sci 86, 577.

KHAFIPOOR E., KRAUSE D.O., PLAIZIER J.C., 2007. Induction of subacute ruminal acidosis (SARA) by replacing alfalfa hay with alfalfa pellets does not stimulate inflammatory response in lactating dairy cows. Poult Sci (Suppl 1), 654.

KLEEN J.L., HOOIJER G.A., REHAGE J., NOORDHUIZEN J.P., 2003. Subacute ruminal acidosis (SARA): a review. J Vet Med A Physiol Pathol Clin Med 50, 406-414.

KRAJCARSKI-HUNT H., PLAIZIR J.C., WALTON J.P., SPRATT R., MCBRIDE B.W., 2002. Effect of subacute ruminal acidosis on *in situ* fiber digestion in lactating dairy cows. J Dairy Sci 85, 570-573.

KRAUSE M.K., OETZEL G.R., 2006. Understanding and preventing subacute ruminal acidosis in diary herds: a review. Anim Feed Sci Technol 126, 215-236.

KREHBIEL C.R., BRITTON R.A., HARMON D.L., WESTER T.J., STOCK R.A., 1995. The effect of ruminal acidosis on volatile fatty acid absorption and plasma activities of pancreatic enzymes in lambs. J Anim Sci 73, 3111-3121.

KYAW-TANNER M., POLLITT C.C., 2004. Equine laminitis: increased transcription of matrix metalloproteinase-2 (MMP-2) occurs during the developmental phase. Equine Vet J 36, 221-225.

LACHMANN G., SIEBERT H., 1980. Die Bestimmung des Säure-Basen-Status in den Erythrocytten und im Lebergewebe beim Rind. Monatshefte der Veterinär-Medizin 35, 384-388. [In German].

LECKLIN A., TUOMISTO J., 1990. Feed intake after inhibition of histamine catabolism. Age Act 30, 216-219.

LINDINGER M.I., HEIGENHAUSER G.J.F., 2008. Lactate is not the only physicochemical contributor to the acidosis of exercise. J Appl Physiol 105(1), 363-367.

MEYERHOF O., LOHMANN K., 1926. Über Atmung und Kohlehydratumsatz tierischer Gewebe. III. Über den Unterschied von d- und l-milchsäure für Atmung und Kohlehydratsynthese im Organismus. Biochemische Zeitschrift Band 171, 421-435. [In German].

MGASA M.N., ARNBJERG J., 1993. Influence of diet on forestomach structure and occurrence of digestal diseases in adult goats. Small Rum Res 10, 63-73.

MUNGALL B.A., KYAW-TANNER A.M., POLLITT C.C., 2001. *In vitro* evidence for a bacterial pathogenesis of equine laminitis. Vet Microbiol 79, 209-223.

NAKAMURA T., UENO Y., GODA Y., NAKAMURA A., SHINJO K., NAGAHISA A., 1997. Efficacy of a selective histamine H_2 receptor agonist, dimaprit, in experimental models of endotoxin shock and hepatitis in mice. Eur J Pharmacol 322, 83-89.

NIKOLOV Y., 1996. Comparative biochemical and hormonal studies on experimental acute lactic acidosis in ruminants. Vet Arhiv 66, 43-49.

NOCEK J.E., 1997. Bovine acidosis: implications on laminitis. J Dairy Sci 80, 1005-1028.

NORDLUND K.V., GARRET E.F., 1994. Rumenocentesis: a technique for collecting rumen fluid for the diagnosis of subacute rumen acidosis in dairy herds. Bov Pract 28, 109-112.

NORDLUND K.V., GARRETT E.F., OETZEL G.R., 1995. Herd-based rumenocentesis: a clinical approach to the

diagnosis of subacute rumen acidosis. Comp Contin Edu Pract Vet 17, S48-S56.

NORDLUND K.V., COOK N.B., OETZEL G.R., 2004. Investigation strategies for laminitis problem herds. J Dairy Sci 87, E27-E35.

OETZEL G.R., 2003. Subacute ruminal acidosis in dairy cattle. Adv Dairy Technol 15, 307-317.

OLSSON G.C., BERGSTEN C., WIKTORSSON H., 1998. The influence of diet before and after calving on the food intake, production and health of primiparous cows, with special reference to sole haemorrhages. J Anim Sci 66, 75-86.

PATRA R.C., LAL S.B., CHATTOPADHYAY S.K., SWARUP D., 1995. Clinical and pathological changes in experimental ruminal acidosis in sheep. Ind J Anim Sci 65, 423-425.

PATRA R.C., LAL S.B., SWARUP D., 1996. Biochemical profile of rumen liquor, blood and urine in experimental acidosis in sheep. Small Rum Res 19, 177-180.

PHILLIPSON A.T., McANALLY R.A., 1942. Studies on the fate of carbohydrates in the rumen of the sheep. J Exp Biol 19, 199-214.

PLAIZIER J.C., KEUNEN J.E., WALTON J.P., DUFFIELD T.F., MCBRIDE B.W., 2001. Short communication: effect of subacute ruminal acidosis on in situ digestion of mixed hay in lactating dairy cows. Canadian J Anim Sci 81, 421-423.

PLAIZIER J.C., KRAUSE D.O., GOZHO N., MCBRIDE B.W., 2008. Subacute rumimal acidosis in dairy cows, the physiological causes, incidence, and consequences. Vet J 176, 21-31.

PRENTICE D.L., 2000. Ionophores: modes of action and use in the prevention of ruminal acidosis and subacute ruminal acidosis. MS thesis. University of Wisconsin-Madison, Madison, WI, USA.

PULINA G., 2004. Dairy sheep nutrition. CABI Publishing, Wallingford, UK.

PUNTENNEY S.B., WANG Y.Q., FORSBERG N.E., 2003. Mycotic infections in livestock: recent insights and studies on etiology, diagnostics and prevention of hemorrhagic bowel syndrome. Available in: http://cals-cf.calsnet.arizona.edu/animsci/ansci/swnmc/papers/2003/forsberg.pdf.

RADOSTITS O.M., BLOOD B.C., GAY C.C., 1994. Acute carbohydrate engorgement of ruminants (rumen overload). In: Veterinary medicine (Radostits O.W., Blood D.C., Gay C.C., eds). WB Saunders, Philadelphia, PA, USA. pp. 262-269.

RAGFAR, 2007. Ruminal acidosis-aetiopathogenesis, prevention and treatment. Reference Advisory Group on Fermentative Acidosis of Ruminants, Australian Veterinary Association, Australia.

RAWN J.D., 1989. Biochemistry. Towson St Univ, Neil Paterson Publ, Carolina Biological Supply Company, Burington, NC, USA.

REBHUN W.C., 1995. Abdominal diseases. In: Diseases of dairy cattle (Rebhun W.C., ed). Williams and Wilkins, Media, PA, USA. pp. 106-154.

ROSSI R., DEL PRETE E., SCHARRER E., 1998. Effects of histamine H1 receptors on the feeding and drinking patterns in pygmy goats. J Dairy Sci 81, 2369-2375.

ROWE J.B., 1997. Acidic gut syndrome': is it a problem for animal and humans? In: Recent advances in animal nutrition in Australia 97 (Corbett J.L., Choct M., Nolan J.V., Rowe J.B., eds). University of New England, Armidale, Australia. pp. 47-54.

ROWE J.B., WINSLOW S.G., MURRAY P.J., 1989. Effect of basal diet and feed additives on the susceptibility of sheep rumen fluid to lactic acid production. Asian-Aust J Anim Sci 2, 346-348.

RUEGG P., 2000. Hooves: a laminitis history book. Proc Annu Conf Am Assoc Bov Pract 33. pp. 69-74.

RYAN R.K., 1964. Concentrations of glucose and low-molecular-weight acids in the rumen of sheep changed gradually from a hay to a hay plus grain diet. Am J Vet Res 25, 653-659.

SEN M.M., MISHRA S.K., CHOUDHARY P.C., 1982. Clinicotherapeutic aspects of acute ruminal acidosis in goats. Indian J Vet Med 2, 25-32.

SHI Y., WEIMER P.J., 2002. Response surface analysis of the effects of pH and dilution rate on *Ruminococcus flavefaciens* FD-1 in cellulose-fed continuous culture. Appl EnvironMicrobiol 58, 2583-2591.

SLYTER L.L., 1976. Influence of acidosis on rumen function. J Anim Sci 43, 910-929.

STONE W.C., 2004. Nutritional approaches to minimize subacute ruminal acidosis and laminitis in dairy cattle. J Dairy Sci 87(E Suppl), E13-E26.

UNDERWOOD W.J., 1992. Rumen lactic acidosis. Part II. Clinical signs, diagnosis, treatment, and prevention. Compendium for continuing education for the practicing veterinarian. Food Anim 14, 1265-1270.

VESTWEBER J.G.E., LEIPOLD H.W., 1974. Experimentally induced ovine ruminal acidosis: pathological changes. Am J Vet Res 35, 1537-1540.

VIGNOLA A.M., MERENDINO A.M., CHIAPPARA G., CHANEZ P., PACE E., SIENA L., PROFITA M., BOUSQUET J., BONSIGNORE G., 1997. Archivio Monaldi per le malattie del torace 52, 83-85. [In Italian].

WALDRON M.R., NISHIDA T., NONNECKE B.J., OVERTON T.R., 2003. Effect of lipopolysaccharide on indices of peripheral and hepatic metabolism in lactating cows. J Dairy Sci 86, 3447-3459.

WALSHA K., O'KIELYA B.P., TAWEELA H.Z., MCGEEA M., MOLONEYA A.P., BOLANDB ATEAGASC T.M., 2009. Intake, digestibility and rumen characteristics in cattle offered whole-crop wheat or barley silages of contrasting grain to straw ratios. Anim Feed Sci Technol 148(2-4), 192-213.

WEINGARTEN H.P., 1996. Cytokines and food intake: the relevance of the immune system to the student of ingestive behavior. Neurosci Biobeh Rev 20, 163-170.

WERLING D.F., SUTTER M., ARNOLD G., KUN P.C., TOOTEN E., GRUYS M., KREUZER W., LANGHANS W., 1996. Characterization of the acute phase response of heifers to a prolonged low dose infusion of lipopolysaccharide. Res Vet Sci 61(3), 252-257.

XU Y., DING Z., 2006. A model for exploring lactic acidosis: 2. Model valuation and validation. Belg J Zool 136(2), 125-135.