Mechanisms of Acid Absorption in the Rumen and Impacts on Subacute Rumen Acidosis

Gregory B. Penner[a,1], and Jörg R. Aschenbach[b]
[a]Department of Animal and Poultry Science, University of Saskatchewan
[b]Institute of Veterinary Physiology, Free University of Berlin

Introduction

A distinguishing feature of ruminants is that they rely on anaerobic fermentation of feeds in the rumen and reticulum (collectively termed the reticulo-rumen) to supply metabolizable energy in the form of short-chain fatty acids **(SCFA)** and metabolizable protein in the form of microbial protein. While the production of SCFA is a nutritionally desired effect, excessive rates of SCFA production and their subsequent dissociation in ruminal fluid can lead to a reduction in ruminal pH and the onset of ruminal acidosis. This is important as the production of SCFA can be substantial. For example, Sutton et al. (2003) measured total SCFA production for Holstein cows fed moderate (40%) or high concentrate (90%) diets reporting that production equated to 79 and 90 mol/d, respectively.

Ruminal acidosis is a common and severe digestive disorder in dairy (Penner et al., 2007; Penner and Oba, 2009) and feedlot cattle (Bevans et al., 2005; Wierenga et al., 2010). Ruminal acidosis only occurs when the rate of acid production exceeds the rate at which acid can be removed from the rumen via neutralization and clearance. For convenience, static ruminal pH thresholds are commonly used to distinguish between the acute (pH < 5.2) and sub-acute classifications of ruminal acidosis (pH < 5.8; Penner et al., 2007). However, in reality, the severity of ruminal acidosis varies on a continuum from sub-acute to acute. As ruminal pH decrease to values below the optimum for ruminal fermentation, negative changes in the ruminal microbial composition and activity, and epithelial function occur (**Figure 1**). For the context of this paper, ruminal acidosis will be considered to occur when ruminal pH < 5.8, and acute ruminal acidosis when pH < 5.2. Although, more severe depressions in ruminal pH may be required to elicit changes in ruminal epithelial function (Gaebel and Martens, 1998; Aschenbach and Gabel, 2000; Penner et al., 2010), the use of pH 5.8 as a threshold encompasses the effect of low pH on fiber digestion as well as the risk for epithelial damage.

The vast majority of previous research has focused on promoting chewing activity to increase saliva production in an effort to neutralize acidity in the ruminal contents. While it is clear that saliva provides an essential source of buffers (primarily bicarbonate) to the rumen, quantitative estimates have shown that saliva alone, only accounts for approximately 30% of the total ruminal buffering capacity (Allen, 1997). From these estimates, it is clear that there must be other strategies to buffer ruminal pH

[1] Contact at: Department of Animal and Poultry Science, 6D18 Agriculture Building, 51 Campus Drive, Saskatoon, Saskatchewan, Canada, S7N 5A8; Phone: (306) 966-4219; Fax (306) 966-4151; Email greg.penner@usask.ca

in order to maintain optimal conditions for ruminal fermentation and animal health and productivity. One such possibility is the absorption of SCFA across the rumen wall. In fact, using the same quantitative estimates as above, it is clear that absorption of SCFA has a central role in acid removal from the rumen (Allen, 1997; Penner et al., 2009a; Aschenbach et al., 2010) accounting for up to 53% of the total proton removal (Gäbel et al., 1991; Allen, 1997). The purpose of this paper is to describe the current understanding on the mechanisms of SCFA absorption and how absorption of SCFA contributes to the stabilization of ruminal pH.

Mechanisms of SCFA Absorption and the Implications on Proton Movement

Mechanisms of SCFA Absorption

Early experiments using anesthetized sheep in which the rumen was isolated from the remainder of the digestive tract by ligatures showed that SCFA were absorbed across the ruminal wall (Danielli et al., 1945, Ash and Dobson, 1963). Despite early studies noting the appearance of bicarbonate and carbon dioxide in the rumen contents (Masson and Phillipson, 1951; Ash and Dobson, 1963) or a rapid increase in pH (Dijkstra et al., 1993) corresponding to SCFA absorption, absorption has to a large extent been thought to occur via passive diffusion (Dijkstra et al.,1993; López et al., 2003; Graham et al., 2007). This proposed mechanism was largely based upon the finding that only undissociated SCFA were permeable across lipid bilayers such as the ruminal epithelium (Walter and Gutknecht, 1986; Gäbeland Aschenbach, 2002). However, there are numerous limitations for the model suggesting near complete passive diffusional absorption of SCFA. For example, based upon the pKa for SCFA and pH values that are commonly measured in commercial and research settings (pH > 5.8; Krause and Oetzel, 2006, Penner et al., 2007; Penner and Oba, 2009), more than 90% of the SCFA would be in the dissociated state. Thus, rates of absorption would be expected to be extremely slow. This notion was counteracted by the hypothesis that there could be an acidic pH microclimate on the luminal side of the ruminal epithelia (Graham and Simmons, 2005). However, studies have found that when measured *in vitro*, the pH on the surface of the epithelia ranged between 7.47 and 7.68 depending on the incubation conditions and was thus even more alkaline than the bulk incubation buffer (pH 7.4) (Leonhard-Marek et al., 2006). Limitations to the model of exclusive passive diffusion also extend to differences for the lipophilicity of individual SCFA. Strictly speaking, it would be expected that the fractional absorption rates would follow butyric acid > propionic acid > acetic acid (Walter and Gutknecht, 1986). However, similar fractional absorption rates have been reported among SCFA *in vitro* (Aschenbach et al., 2009) and when differences are found (Dijkstra et al., 1993; López et al., 2003), they are not consistent with the theoretically predicted increase in lipophilicity (e.g. butyric acid is 14 times more lipophilic than acetic acid; Walter and Gutknecht, 1986). This is in direct contrast with ruminal SCFA production and concentration where quantitatively production follows acetate > propionate > butyrate (Sutton et al., 2003).

Based upon the limitations listed above, numerous studies have been conducted to determine the mechanisms involved in SCFA absorption across the rumen. A partial

model showing the current understanding and how the absorption of SCFA contributes to the stabilization of ruminal pH is depicted in **Figure 2**. It is important to note that while not the only mechanism involved, SCFA can be absorbed via passive diffusion with the proportion absorbed accounting for between 28 to 60% of the acetate, and 69 to 75% of the butyrate when measured *in vitro* (Penner et al., 2009a). These data correspondingly also indicate that non-diffusional uptake accounts for up to 72% of the acetate, and 31% of the butyrate. Proportionally, the reliance on bicarbonate-dependent mechanisms is approximately 52% of the total acetate uptake (Ash and Dobson, 1963; Gäbel et al., 1991; Penner et al., 2009a). Thus, it is clear that protein mediated pathways contribute substantially to the absorption of SCFA.

Pathways of SCFA Absorption and the Removal of Protons from the Rumen

When SCFA are absorbed via passive diffusion, 1 proton is removed from the ruminal contents; however, upon appearance in the cytosol, SCFA will rapidly dissociate. The proton released then needs to be expelled from the cell in order to maintain intracellular pH and tissue integrity. Transporters involved in the regulation of intracellular pH include the sodium/hydrogen exchangers **(NHE)** which can export protons back to the lumen or into extra-cellular spaces. In addition to NHE, the monocarboxylate transporter **(MCT)** has been shown to be localized on the basolateral membrane (blood facing; Graham et al., 2007) and can facilitate the removal of a proton along with metabolic end-products of SCFA metabolism such as ketone bodies and lactate (Müller et al., 2002; Kirat et al., 2006). Thus, the direction of proton export has major implications for whether passive diffusion contributes to the stabilization of ruminal pH. For example, if the proton was exported back into the rumen contents as a strategy to maintain intracellular pH, there would be no net proton removal. With such a scenario, this would indicate that there is no direct contribution towards the stabilization of ruminal pH via passive diffusion. Interestingly, the expression and activity of NHE in ruminal epithelia increase when highly fermentable diets are fed (Etschmann et al., 2009; Yang et al., 2009). However, due to the complexity of the transport mechanisms involved and the regulation of their activity, it is very difficult to quantify or predict the proportion of protons recycled back to the lumen relative to those that account for permanent removal from the ruminal contents. That said, it is clear that passive diffusion does contribute to the removal of protons from the rumen under most circumstances (Penner et al., 2009a).

Transporters promoting luminal absorption of SCFA include a variety of anion exchangers (Bilk et al., 2005; Aschenbach et al., 2009; Penner et al., 2009a). With anion exchange, dissociated SCFA are exchanged for bicarbonate in an electro-neutral transport process (see **Figure 2**). This mechanism provides a source of bicarbonate to the ruminal environment where it can neutralize a proton via the carbonic anhydrase reaction producing carbon dioxide and water. Driving forces for bicarbonate-dependent transport include the concentration of ruminal SCFA and ruminal pH. In fact, the bicarbonate-dependent SCFA absorption increases with increasing luminal SCFA concentration and with decreasing ruminal pH (Aschenbach et al., 2009). Thus, it appears that this transport process is crucial in terms of helping to regulate ruminal pH (Penner et al., 2009a).

Evidence Linking SCFA Absorption to the Stabilization of Ruminal pH

It is not a new concept that absorption of SCFA can contribute to the stabilization of ruminal pH. In fact, early studies (Masson and Phillipson, 1951; Ash and Dobson, 1963; Gäbel et al., 1991) already pointed to the accumulation of bicarbonate in ruminal contents and an increase in the incubation buffer pH (Dijkstra et al.,1993) with the absorption of SCFA. For example, although it was not the objective of the study, Dijkstra et al. (1993) reported that pH increased to 7.1, 8.0, 8.2, and 8.2 from initial pH values of 4.5, 5.4, 6.3, and 7.2, respectively, when artificial buffers were placed in the evacuated and washed rumen of dairy cows. Moreover, several reviews (Allen, 1997; Gäbel et al., 2002; Aschenbach et al., 2010) have indicated that on a theoretical basis, SCFA absorption should help to stabilize ruminal pH. Despite the number of publications proposing this hypothesis, until recently, there were a limited amount of data proving this concept and there were no data demonstrating how the type of SCFA or mechanism of absorption affected ruminal pH homeostasis.

In dairy cattle, Resende Júnior et al. (2006) reported that ruminal pH was positively related (r^2 = 0.43) to the fractional rate of SCFA clearance (sum of absorption and passage) from the rumen. In that study, they further evaluated whether the effect on pH was due to absorption of SCFA across the rumen wall or the passage of SCFA into the omasum, finding that both mechanisms were positively related to ruminal pH. In another study, Penner et al. (2009b) reported negative correlations between the expression of a number of genes involved in SCFA metabolism and the severity of ruminal acidosis for dairy cows fed a diet containing 64% concentrate. While these studies (Resende Júnior et al., 2006; Penner et al., 2009b) showed direct relationships between ruminal pH or the severity of ruminal acidosis and the absorption of SCFA or indicators for intra-epithelial metabolism of SCFA, they cannot provide insight regarding the cause and effect nor can they elucidate how the pathway of SCFA and type of SCFA affect ruminal pH.

To address these limitations, we conducted a study to determine the relationship between the uptake of SCFA and the severity of ruminal acidosis when induced using an oral glucose drench (Penner et al., 2009a). Based on the variation in ruminal pH observed following the drench, we assigned animals to 1 of 2 classifications; non-responders **(NR)** or responders **(RES)** and compared the uptake of acetate and butyrate, measured *in vitro*, between the 2 classifications and a group that was not exposed to an acidotic challenge **(SHAM)**. A crucial finding in this study was that although the duration that pH was < 5.8 during the 3 h acidotic challenge differed between sheep classified as NR (67.8 min), RES (153 min) and SHAM (1.1 min), the uptake of acetate and butyrate measured *in vitro* did not differ between RES and SHAM sheep. These data indicate that, under the conditions imposed, the acidotic challenge did not negatively affect absorptive function and thus allowed us to determine whether differences in the absorptive function between NR and RES accounted for their differing susceptibility to ruminal acidosis during the acidotic challenge. Interestingly, we found that epithelia from NR sheep had a greater rate of total acetate and butyrate uptake than RES (**Figure 3**). Retrospective correlation analysis also showed that acetate and

butyrate uptake was positively related to the mean pH prior to the acidotic challenge. This study provided comprehensive data demonstrating that the rate of acetate and butyrate uptake has a substantial effect on ruminal pH homeostasis.

In that same study (Penner et al., 2009a) we showed that not only was total uptake greater for NR than RES, but the main mechanisms facilitating acetate and butyrate uptakes were different between NR and RES. For acetate, the protein-mediated uptake, including the bicarbonate-dependent mechanism, was greater for NR than RES (**Figure 3**). As mentioned above, with this mechanism bicarbonate secretion and acetate absorption are coupled. Interestingly, for butyrate, bicarbonate-independent (passive diffusion) uptake was higher for NR than RES. Collectively these data indicate that the pathway of SCFA absorption may differ based upon the type of SCFA and thus the relative contribution towards the stabilization of ruminal pH may also differ. For example, acetate is not as lipophilic as butyrate and thus protein-mediated pathways contribute substantially towards its uptake. This is important as the bicarbonate-dependent pathway would also provide bicarbonate to buffer the rumen contents (Aschenbach et al., 2009). In contrast, butyrate has a greater potential for diffusional uptake (Walter and Gutknecht, 1986). Thus, factors promoting a concentration gradient between the rumen, cytosol, and blood should promote absorption (Gäbel et al., 2002). The suggestion that intracellular metabolism enhances butyrate absorption is in alignment with Gäbel et al. (2001) and previously reported negative correlations between the expression of genes involved in butyrate metabolism and the severity of ruminal acidosis (Penner et al., 2009b). Furthermore, we found that NR sheep had greater serum BHBA (a metabolite of butyrate metabolism) than RES sheep after the 180 min acidotic challenge (Penner et al., 2009a). The increase in serum BHBA may also indicate that for butyrate, metabolism to ketone bodies and export from the cell via MCT may help to regulate ruminal pH as this transport mechanisms also exports a proton from the cytosol.

Although, we only evaluated acetate and butyrate, it could be expected that these results would also extend to other SCFA. Specifically, we would expect that propionate would have a high reliance on bicarbonate-dependent transport as for acetate (Aschenbach et al., 2009). Based on the current data available it is evident that SCFA absorption helps to stabilize ruminal pH and that the relative effect of individual mechanisms (passive diffusion, bicarbonate-dependent transport) for absorption differs based on the SCFA (acetate, propionate, and butyrate) absorbed.

Nutritional Management to Alter SCFA Absorption

While it may be an interesting finding that SCFA absorption is related to the stabilization of ruminal pH, the relevance of this finding for industry application also requires investigation. There are two approaches that could be implemented to capitalize on the findings that SCFA absorption is positively related to ruminal pH homeostasis. Firstly, an attempt to link the susceptibility to sub-acute ruminal acidosis to a genetic marker or several markers could be attempted. If successful, this would allow for the identification of individual cattle with enhanced SCFA absorption relative to

their herd-mates and thus reduced susceptibility to subacute ruminal acidosis **(SARA)**. However, one must realize that SARA is a multi-factorial disorder that is affected by, *inter alia*, the microbial population, mechanisms for absorption and metabolism, saliva production and composition, and rumen motility. Another more practical approach would be to design nutritional strategies that enhance epithelial function. This approach is a herd-based approach and is most likely of the two to succeed.

Factors Negatively Affecting the Potential for SCFA Absorption

Past *in vivo* and *in vitro* studies have clearly shown that short-term feed withdrawal (48 h) has negative effects on SCFA absorption in the rumen without corresponding decreases in the absorptive surface area (Gäbel et al., 1993; Gäbel and Aschenbach, 2002). In particular, Gäbel et al. (1993) showed that the net absorption of acetate, propionate, and butyrate was only 56, 44, and 43% as much as sheep not exposed to feed withdrawal. This reduction in absorption in combination with reduced SCFA concentration occurring with short-term feed deprivation could have substantial impacts on the nutrient status of individual cattle as well as the risk for acidosis upon re-feeding. It should be noted that past studies have only investigated the effect of complete feed deprivation in the short-term and that there is a paucity of data regarding the effect of feed restriction which is likely more representative and relevant to industry situations. For example, as parturition approaches, dairy cattle decrease DMI by approximately 30% (Hayirli et al., 2002) and then rapidly increase DMI post-partum. To our knowledge, no studies have linked SCFA absorption and ruminal pH during the transition period, but Reynolds et al. (2003) reported that the portal appearance of total SCFA and metabolites linearly increased from d 19 pre-partum until d 83 post-partum. The lowest rates that occurred post-partum were within the first 11 and 21 d relative to parturition. These results are in agreement with those of Penner et al. (2007) showing that the severity of ruminal acidosis peaked around d 17 post-partum. Other industry-relevant examples where feed intake may be compromised include heat stress, during transportation, and with illness. Research is needed to elucidate how the severity and duration of feed restriction alters SCFA absorption and ruminal pH upon resumption to pre-restriction intakes.

Nutritional Strategies to Enhance SCFA Absorption

The vast majority of past studies have focused on enhancing the absorptive surface area as a means to increase SCFA absorption (Dirksen et al., 1985, Penner et al., 2006). It has been shown repeatedly that ruminants fed high-concentrate diets have greater rates of SCFA absorption (Dirksen et al., 1985; Gäbel et al., 1991) which can be partially attributed to increased absorptive surface area. However, ruminants fed high-concentrate diets are also at greater risk for ruminal acidosis and typically have lower ruminal pH (Dohme et al., 2008; Penner et al., 2009b). Unfortunately, few studies have investigated strategies to further enhance SCFA absorption.

One strategy to enhance SCFA uptake would be by gradual exposure to higher SCFA concentration associated with dietary transition (Dirksen et al., 1985; Bannink et al.,2008) or by exposing epithelia to greater butyrate concentrations (Sakata and Tamate, 1978; Sakata et al, 1980) through strategic supplementation (DeFrain et al.,

2004). In an attempt to increase the absorptive capacity of the ruminal epithelium, Sehested et al. (2000) fed cattle diets with the same forage:concentrate ratio but altered the feeding strategy. In this study, one group was fed concentrate in morning feeding and silage in the afternoon feeding while the other group received a mixed diet at both feedings. Feeding the concentrate and silage separate was designed to transiently increase the SCFA concentration in the rumen in hope to stimulate epithelial function. Their results show that this feeding strategy did increase the net butyrate absorption across the ruminal epithelia but, this feeding strategy is not recommended due to challenges with feeding management with cattle in group-housed settings.

In another study (Wilson, D. J., T. Mutsvangwa, and G. B. Penner, unpublished), sheep were fed diets containing 90% concentrate and 10% forage supplemented with 0, 1.25, or 2.50% butyrate (DM basis). The objective of this study was to determine if providing additional butyrate could be used as a strategy to enhance the absorptive function. We found that providing additional butyrate increased the ruminal butyrate concentration by 6.3 and 20.8 m*M* for lambs fed 1.25% and 2.50% compared to those fed 0% butyrate which had a ruminal butyrate concentration 5.6 m*M*. However, under the conditions imposed, we found that providing supplemental butyrate actually decreased the mucosal-to-serosal flux of butyrate measured *in vitro* (**Figure 4**). Reasons for these findings are still not fully understood but it may suggest that this strategy may not be effective in finishing-type diets.

Conclusions

Short-chain fatty acid absorption clearly helps to stabilize ruminal pH by either removing protons with passive diffusion or by the secretion of bicarbonate with anion exchange mechanisms. Interestingly, the relative contribution of individual pathways differs based on the type of SCFA absorbed. Future research is needed to determine how nutritional management can be used to enhance the absorptive function of the ruminal epithelia in an effort to mitigate ruminal acidosis.

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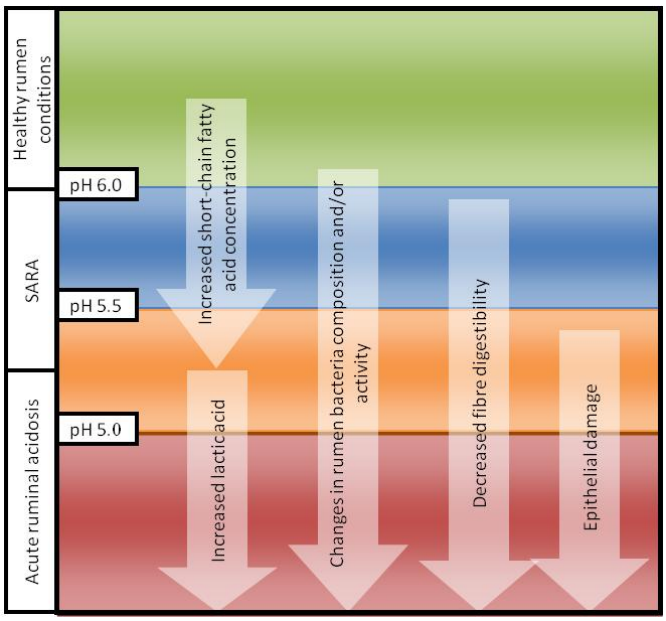

Figure 1. Relationship between ruminal pH and the associated changes in the ruminal environment and ruminal epithelial function (reproduced from Penner and Beauchemin, 2010).

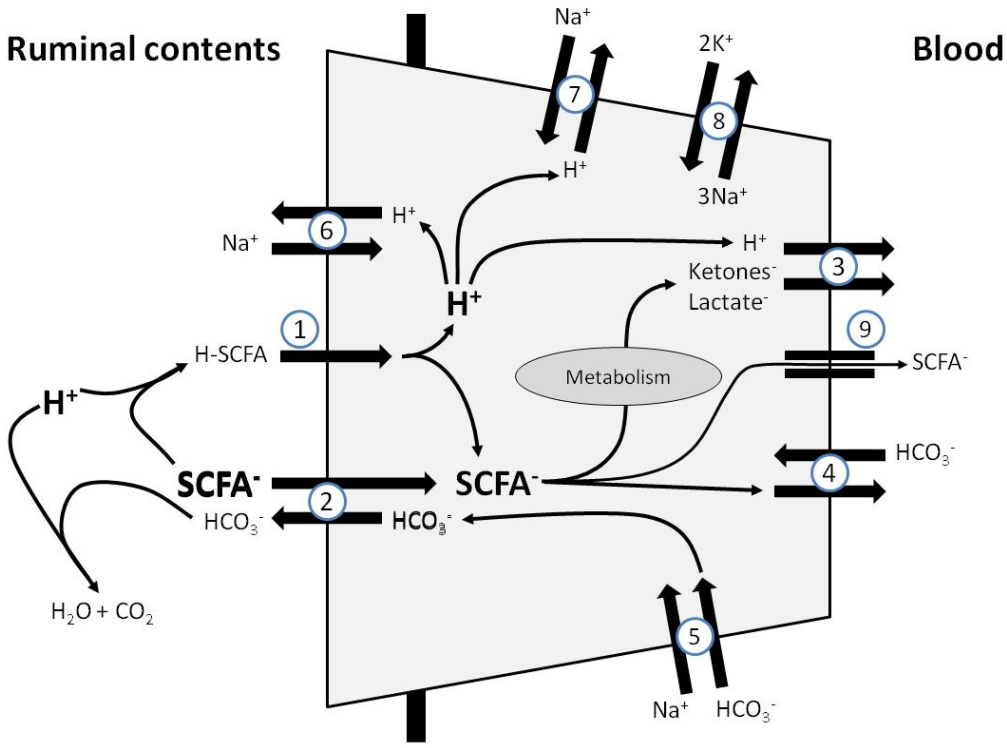

Figure 2. Partial model depicting the current understanding for SCFA absorption in relation to the stabilization of ruminal pH. 1) Diffusional absorption of SCFA facilitates the removal of a proton associated with the SCFA. This proton will rapidly dissociate in the cytosol where it can be exported by sodium/hydrogen exchanges (6, 7) or coupled with metabolites of SCFA (e.g. ketone bodies and lactate) via the monocarboxylate transporter (3) or a basolateral ion channel (9). Dissociated SCFA can be absorbed in an anion exchange mechanism thereby providing a source of bicarbonate to the ruminal contents (2). This bicarbonate can then neutralize a proton through the carbonic anhydrase reaction. The bicarbonate supply to the epithelia is derived from blood (4, 5). Note, the model does not show the structural complexity of the ruminal epithelia including the number of strata and cells within strata. Adapted from Aschenbach et al. (2010).

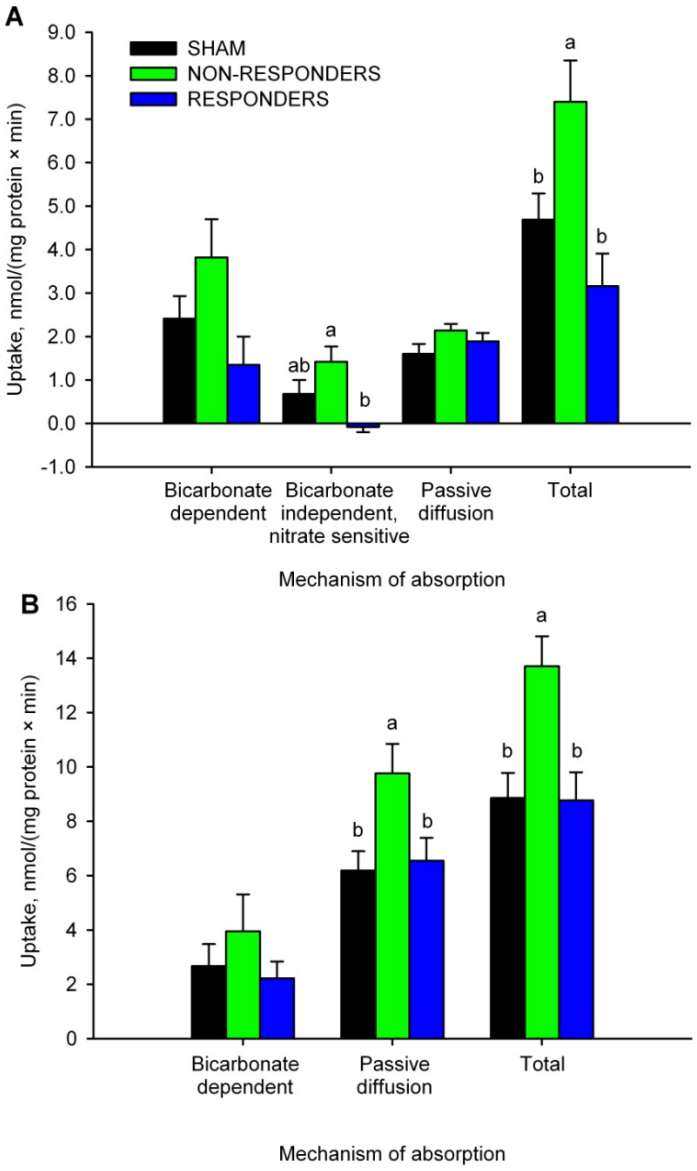

Figure 3. Mechanisms for the apical uptake of acetate (A) and butyrate (B) by the isolated ruminal epithelia harvested from sheep not exposed to ruminal acidosis (SHAM) or sheep exposed to ruminal acidosis using a 2.2 *M* glucose drench. Based on the ruminal pH response during the 3 h period following the drench, sheep were classified as NON-RESPONDERS if they did not experience ruminal acidosis or RESPONDERS if they experienced ruminal acidosis. Means within a mechanism of absorption with uncommon letters differ significantly ($P < 0.03$). Adapted from Penner et al. (2009a).

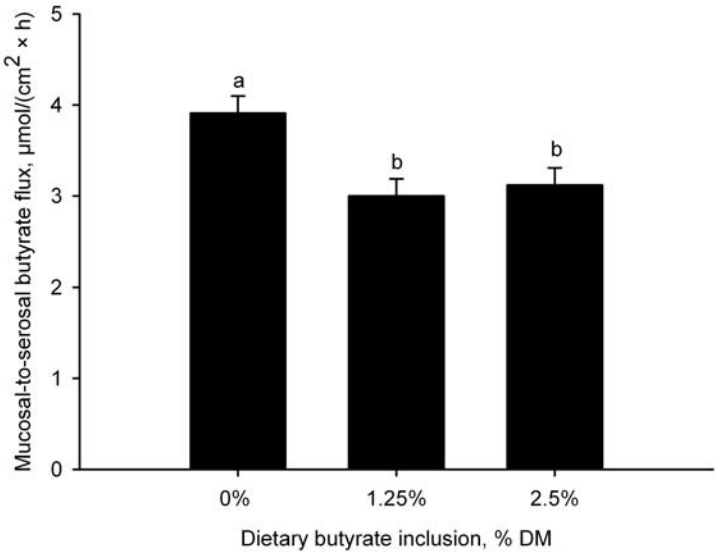

Figure 4. Effect of dietary butyrate inclusion level on the mucosal-to-serosal flux of butyrate across the isolated ruminal epithelia of sheep. Columns with uncommon letters differ significantly (P = 0.013). Data from Wilson, D.J., T. Mutsvangwa, and G.B. Penner (unpublished).

SESSION NOTES