



Impact of Subacute Ruminal Acidosis (SARA) on Ruminal Microbiome, Lipopolysaccharide and Bioamine and Rumen Epithelial Health of Dairy Cows

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Abstract

Maximizing milk yield without impairing host health is a great challenge for dairy industry. However, the high concentrate feeding often unavoidably increases the risk of Subacute ruminal acidosis (SARA) in dairy cows, characterized by periodic episodes of low ruminal pH. The economic costs caused by SARA are enormous, while its pathogenesis is not very clear. As the first and the main digestive compartment, the rumen health during SARA has received much research effort in recent years. There are increasing evidences showing that the effects of SARA on rumen are multifaceted and detrimental. To address this issue, this review summarized the impact of SARA induced by high-concentrate feeding on gastrointestinal microbiota, ruminal fermentation, and its role in damage to the ruminal epithelium and host function in dairy cows. Further experimental work is required to elucidate the mechanisms by which high-concentrate feeding induces ruminal epithelial barrier dysfunction, as well as the relationship between ruminal epithelial barrier dysfunction and high concentrate diet-induced metabolic disease, which seem to be of great importance for preventing these diseases.

Keywords: Dairy cows; Microbiome; Lipopolysaccharide; Bioamine; Rumen epithelium

Abbreviations: SARA: Subacute Ruminal Acidosis; LPS: Lipopolysaccharide; VFA: Volatile Fatty Acid; TJS: Tight Junctions

Introduction

The dairy industry in China is developing with unprecedented speed as milk plays an increasingly important part in the Chinese diet. It is estimated that dairy cattle herds increased from 0.493 million to 14.3 million between 1978 and 2014. Meanwhile, average annual milk production per head increased by about 2,800 kg from 1998 to 2014. Milk production is associated with genetics, feeding, and management, among which diet plays a crucial role in regulating milk yield.

In the modern dairy sector, it is common practice to provide high-grain diet and high-quality forage such as alfalfa to increase volatile fatty acid production and further improve milk production. However, China lacks high-quality forage and in 2014 imported 1.005 million tons of alfalfa. Thus, due to the shortage of high-quality forage in China, dairy cows are usually fed a high proportion of concentrate in order to improve milk production. However, high-concentrate feeding could reduce rumen pH and increase the accumulation of VFAs. These changes are usually

coupled with an increased incidence of metabolic diseases, for example Subacute ruminal acidosis (SARA).

SARA is a well-recognized digestive disorder that is an increasing health problem in most dairy herds, with surveys suggesting an incidence of between 19% and 26% in early- and mid-lactation dairy cattle [1]. The problem might be particularly pressing in high-yield dairy herds, as producers respond to the demand for greater milk production by increasing the proportions of grains and lowering dietary fiber, thereby maximizing energy intake. The economic costs associated with SARA are estimated at around US\$ 1.12 per day per affected cow [2]. These losses arise from the negative influence of SARA on rumen fermentation, animal health (e.g. increased risk of lameness) and productivity as well as higher culling rates and lower fertility [2,3]. This study reviews the findings of the National Key Basic Research Program of China (2011CB100801) in the years from 2011 to 2014, on the role of SARA induced by

high-concentrate feeding on gastrointestinal microbiota, ruminal fermentation, and its role in damage to the ruminal epithelium and host function in dairy cows.

SARA and rumen microbiome

Several studies have examined rumen microbial changes in association with SARA. The most common bacteria detected in the rumen of cattle and steer linked to SARA are *Lactobacillus spp.* and *Streptococcus bovis* [4]. The dominant bacterial phyla include Firmicutes, Bacteroidetes, and all subgroups of Proteobacteria [5]. In recent years, we used pyrosequencing methods to monitor changes in the composition and structure of rumen bacterial communities [6]. Our findings revealed that, at a high taxonomic level, the percentages of Proteobacteria and Bacteroidetes were reduced by high-concentrate feeding, whereas Firmicutes and Actinobacteria were more abundant in the SARA group than in the control group. At the genus level, the SARA group showed lower abundances of *Prevotella*, *Treponema*, *Anaeroplasma*, *Papillibacter*, *Acinetobacter*, and unclassified populations including unclassified Lentisphaerae, and unclassified bacteria; but higher proportions of *Ruminococcus*, *Atopobium*, unclassified Clostridiales, and Bifidobacterium. High-concentrate feeding reduced the diversity of the rumen microbial community. Taken together, our data showed that the diversity, richness, and composition of rumen bacterial communities differed between groups fed a control diet or a SARA-inducing diet.

SARA and rumen free LPS and biogenic amines

Lipopolysaccharide (LPS) is a cell wall component of all Gram-negative bacteria, which is the predominant bacterial group in the rumen. Previous studies have shown that feeding high levels of grain to goats or dairy cattle leads to a decline in ruminal pH, causing death and cell lysis of Gram-negative bacteria, resulting in higher concentration of free LPS in the rumen [7,8]. However, although many studies have reported changes in LPS levels under different feeding conditions, there is presently no microbial model relating changes in rumen Gram-negative bacteria population with ruminal accumulation of LPS. Our recent study showed that high-grain diet-induced SARA significantly increased ruminal free LPS levels and altered the composition of the ruminal microbiota, with increased abundance of Firmicutes and Actinobacteria and reduced Bacteroidetes and Proteobacteria (Gram-negative species), compared with animals fed a control diet [6]; furthermore, there was a highly significant negative correlation between the abundance of Bacteroidetes and the LPS level. Our data revealed that low rumen pH in cattle fed the SARA could lead to death and lysis of Gram-negative rumen bacteria, especially Bacteroidetes spp., ultimately resulting in increased concentration of free LPS in the rumen.

Biogenic amines are low molecular weight organic bases present in all organisms. The most common forms are tyramine, putrescine, histamine, methylamine, and tryptamine. At low concentrations, they are essential for normal growth and

differentiation of cells [9], but in larger quantities (1.4 g per day) they become harmful to humans and livestock [10]. Our data revealed that a higher-concentrate diet encouraged cow rumen fermentation (as indicated by greater VFA production), increased biogenic amine concentration in the rumen and in peripheral blood, and lowered ruminal pH [11]. High-grain feeding also increased the numbers of *Lactobacillus spp.* Correlation analysis indicated that the biogenic amine concentration in peripheral blood was correlated with the levels of ruminal biogenic amines. The results revealed that the increase in numbers of *Lactobacillus spp.* during SARA may be partly responsible for the increasing biogenic amine concentration in the rumen. Further research is needed to understand the role of this biogenic amine in animal physiological activities, especially the inflammatory response.

Rumen function response to LPS

As mentioned earlier, LPS is a component of the cell wall of Gram-negative bacteria and can be released during rapid growth period or when the bacteria are dying. LPS is known to be a highly potent antigen, and stimulates an intense host inflammatory response that can be induced experimentally by the administration of purified LPS [12]. It has been demonstrated that intravenous infusion of LPS reduced milk yield in dairy cattle; the decreased animal performance may, in part, be affected by altered gastrointestinal digestibility, digesta passage rate, or ruminal fermentation [13,14]. Waggoner, et al. [15] demonstrated that LPS infusion reduced passage rates of gastrointestinal solid and liquid contents. In recent years, we tested the hypothesis that LPS infusion into the blood circulatory system could alter rumen microbiota and rumen metabolism in dairy cattle. Our findings revealed that the relative populations of the phylum Bacteroidetes and the genus *Prevotella* decreased, while that of the phylum Firmicutes increased in response to LPS infusion [16]. The population changes in these specific groups may be partly due to an indirect result of LPS, via changing the rumen pH value. Moreover, our findings confirmed that LPS infusion in the blood circulatory system alters rumen fermentation and leads to a general decrease in fermentative activity. These results imply that translocated LPS during rumen acidosis may aggravate the dysfunction of rumen, resulting in a double detriment to rumen health in dairy cattle.

SARA and rumen epithelial health

Ruminal epithelium plays an important role in physiological functions such as the absorption and transport of nutrients, short-chain fatty acid metabolism, urea cycle, and in barrier function. Previous studies found that ruminal epithelium of sheep and cattle has extensive barrier-forming properties, depending on the multicellular structure (stratum corneum, granulosum, spinosum, and basale) and the junctional complex that establishes a barrier between sometimes hostile external environments and the internal milieu [17-19]. Tight junctions (TJs) located in the middle layers (stratum granulosum and spinosum) play a key role in maintaining the polarity of epithelial cells, regulating the permeability of the epithelial barrier and

preventing the translocation of LPS and other toxins [17,18]. In recent years, we used goats as a ruminant model to characterize the changes in TJ protein expression and distribution in rumen epithelium during high grain feeding [20]. Goats fed a high-grain diet showed profound alterations in ruminal epithelial structure and TJ proteins, depicted by marked epithelial cellular damage and intercellular junction erosion; down-regulation of TJ proteins claudin-4, occluding, and zonulaoccludens-1 mRNA and protein expression; as well as redistribution of claudin-1, claudin-4, and occluding. Furthermore, these changes in TJ proteins in the high-grain group were coupled with the upregulation of mRNA levels for the cytokines TNF- α and IFN- γ in the ruminal epithelia. These results demonstrated for the first time that high grain diet caused disruption of ruminal epithelial TJs that was associated with a local inflammatory response in the rumen epithelium.

Conclusion

The use of a high-concentrate diet is a double-edged sword: it can increase milk production, but can also lead to the accumulation of ruminal metabolites such as VFA, biogenic amines, and change the ruminal environment. The decrease of rumen pH and the accumulation of toxins such as LPS can damage the ruminal epithelial barrier and enable these toxins to shift from the rumen to the blood. Therefore, long-term use of a high-concentrate diet may lead to health risks for dairy cattle. To advance our knowledge, further experimental work is required to elucidate the mechanisms by which high grain feeding induces ruminal epithelial barrier dysfunction, as well as the relationship between ruminal epithelial barrier dysfunction and high grain diet-induced metabolic disease, which seem to be of great importance for preventing these diseases.

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