Advances in Research on the Effects of Subacute Ruminal Acidosis on Rumen Epithelium and Internal Environment in Ruminants: Postprint

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Date: 2018-12-24T00:00:00+00:00

Abstract

Subacute Ruminal Acidosis (SARA) is the most common nutritional metabolic disease in modern intensive ruminant production. SARA is a chronic disease caused by increased concentrate feeding and altered dietary structure, which lead to excessive accumulation of volatile fatty acids in the rumen, decreased ruminal pH, and consequent alterations in the microbial flora. This article primarily introduces two aspects: the effects of SARA on ruminal epithelium and ruminal internal environment, elaborating in detail on changes in ruminal epithelial structure, cell junctions, permeability, and the internal environment, thereby providing theoretical references for in-depth research on SARA.

Full Text

Research Progress on the Effects of Subacute Ruminal Acidosis on Rumen Epithelium and Internal Environment in Ruminants

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Abstract: Subacute ruminal acidosis (SARA) represents the most prevalent nutritional metabolic disorder in modern intensive ruminant production systems. The condition arises from dietary shifts toward increased concentrate levels, which elevate volatile fatty acid (VFA) accumulation in the rumen, depress ruminal pH, and alter microbial flora, culminating in a chronic disease state. This

review synthesizes current knowledge on SARA' s impacts on rumen epithelium and internal environment, detailing alterations in epithelial architecture, cellular junctions, permeability, and ruminal homeostasis to provide a theoretical foundation for advanced SARA research.

Keywords: subacute ruminal acidosis; ruminants; rumen epithelium; cell junctions; permeability; internal environment

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In recent years, rising consumption of dairy and meat products has driven China' s dairy, beef, and mutton industries toward large-scale, intensive production models. To maximize productivity, producers have progressively increased dietary concentrate levels to meet animals' energy demands and enhance performance. However, this practice has substantially elevated the risk of nutritional metabolic diseases, maintaining high incidence rates for conditions including subacute ruminal acidosis (SARA), ketosis, laminitis, and fatty liver [1-2]. Among these, SARA has emerged as particularly prominent and prevalent, representing one of the most damaging and economically consequential diseases in contemporary ruminant production [3]. Prevention, definition, and diagnosis remain challenging due to subtle clinical symptoms and complex etiologies, resulting in substantial livestock industry losses [4]. Therefore, investigating SARA' s pathogenesis, pathological changes, and effective prevention and control strategies is crucial for safeguarding ruminant health and improving production performance.

1 Overview of SARA

SARA is a subclinical disease widely prevalent in rapidly fattening cattle and high-yielding dairy operations, characterized by herd-level outbreaks and high incidence rates [5]. Its hallmark features include low ruminal pH and elevated volatile fatty acid (VFA) concentrations, with high-producing and periparturient dairy cows representing the most susceptible populations [6].

As modern dairy, beef, and mutton production systems pursue greater efficiency, producers have increased the provision of high-concentrate diets. Compared to North America and Europe, China lacks high-quality forage resources. Except for large-scale operations that purchase imported alfalfa and meadow grass, most regions still rely on crop residues as primary roughage, necessitating high levels of starch-rich concentrates to meet nutritional requirements. This situation has increased the incidence of nutritional metabolic diseases, particularly SARA. In Europe, up to 26% of mid-lactation and 19% of early-lactation dairy cows suffer from SARA [7], while annual economic losses from SARA in North American dairy industries reach $500 million to $1 billion [8]. In China, losses are even more severe, primarily through reduced milk yield, decreased product quality, and increased culling and mortality rates [2,4].

Extensive research has advanced SARA diagnosis, treatment, and pathogene-

sis understanding. Proposed toxic mechanisms include endotoxin (lipopolysaccharide) and histamine (HIS) toxicity [3], lactic acidosis, and organic acidosis. However, limited technological capabilities have constrained most dietary SARA research to single rumen metabolites (e.g., lactate, VFA, endotoxin), leaving knowledge gaps regarding the integrated metabolic characteristics and interconnections among different metabolites under varying dietary conditions. Consequently, the occurrence and regulatory mechanisms of SARA in ruminants remain a critical scientific question.

2.1 Effects of SARA on Rumen Epithelial Structure

The rumen epithelium is a stratified squamous structure comprising, from mucosal to serosal surfaces: the stratum corneum (SC), stratum granulosum (SG), stratum spinosum (SS), and stratum basale (SB) [9]. In adult ruminants, stratum corneum cells continuously slough through mechanical friction with ingesta and bacterial colonization, undergoing regular renewal [10]. Tight junctions (TJ) between granulosum cells constitute crucial structures for maintaining mucosal barrier integrity [9]. The basale layer connects to the muscularis and contains fully functional mitochondria, representing the primary metabolic site of the rumen epithelium.

Researchers induced SARA in dairy goats by gradually increasing dietary non-fiber carbohydrate (NFC) to neutral detergent fiber (NDF) ratios, observing significant desquamation and damage to the rumen epithelial stratum corneum, with reduced papilla length, width, and corneum thickness compared to controls [11]. Studies by Yang [12] and Liu [13] reported consistent findings, showing decreased spinosum and total epithelial thickness, significantly reduced granulosum thickness, and diminished papilla length in SARA-affected goats. Building on this work, Cheng [14] examined rumen papillae under 40× light microscopy, revealing that SARA compromised epithelial morphological integrity and caused severe keratinization [Figure 2: see original paper]. Additional studies have confirmed severe structural damage under high-concentrate diets. Steele et al. [15] demonstrated that compared to high-forage diets, high-concentrate feeding caused severe stratum corneum sloughing, gradual disappearance of deep fissures, and reduced thickness of the basale, spinosum, granulosum, and total epithelium. Weng et al. [16] fed single-straw diets with high concentrate levels and observed minimal corneum degeneration, accelerated cell migration in underlying layers, and degraded cellular connections in the granulosum.

2.2 Effects of SARA on Rumen Epithelial Cell Junctions

Rumen epithelial cell junctions in ruminants comprise, from apical to basal membranes: tight junctions (TJ), desmosome junctions (DJ), adhesion junctions (AJ, also called anchoring junctions), and gap junctions (GJ, also called communicating junctions). These structures function cooperatively to ensure rumen epithelial barrier integrity.

2.2.1 Effects on Tight Junctions

Tight junctions represent essential components of the apical junctional complex in epithelial cells, with structures illustrated in [Figure 3: see original paper] [17]. In rumen epithelial cells, tight junctions primarily form ring-like structures at the apical region of the basolateral membrane [17-18]. Tight junctions serve three functions: barrier function—preventing mixing of basolateral membrane proteins with apical domains and blocking harmful substance invasion; gating function—controlling paracellular flux of ions and other solutes; and intercellular communication—transmitting intercellular signals and maintaining physiological homeostasis [19].

Epithelial cells regulate solute and fluid transport through cellular pathways, with barrier function mediated by tight junction proteins at the apical intercellular space that modulate transport of small neutral molecules. Transmission electron microscopy observations in [Figure 4: see original paper] [20] reveal significant ultrastructural changes in SARA-affected goats compared to healthy controls [FIGURE:4-A], including markedly reduced tight junction numbers, blurred structures, enlarged intercellular spaces, mitochondrial degradation in the spinosum layer, and compromised epithelial integrity [FIGURE:4-B].

Tight junctions consist primarily of tight junction-associated proteins, including Claudin family members, Occludin, and Zonula occludens (ZO) family proteins [21-23]. Steel et al. [24] first determined the complete coding sequences of tight junction proteins Claudin-1, Claudin-4, and Claudin-7 in sheep rumen epithelium. Subsequently, Aschenbach et al. [25] reported expression and distribution patterns of Claudin-1, Claudin-4, Claudin-7, Occludin, and ZO-1. Researchers induced SARA in goats with high-concentrate diets and measured increased Claudin-4 gene expression [20], providing mechanistic insight into rumen epithelial permeability changes.

2.2.2 Effects on Desmosome Junctions

Desmosome junction structure is illustrated in [Figure 5: see original paper] [26]. These button-like point structures connect adjacent cells, while hemidesmosomes at the epithelial cell-extracellular matrix interface similarly present as point structures anchoring epithelial basement membranes to the basal lamina, reinforcing cellular connections. Rumen epithelial desmosomes in ruminants reside between the spinosum and granulosum layers, enhancing tissue toughness and providing critical support against mechanical pressure and tension to maintain structural organization.

Desmosomal plaques are dense structures at desmosome junction sites that connect cells. Composed of anchoring proteins linked to intracellular intermediate filaments, desmosomes interconnect intermediate filaments between cells, forming robust intercellular connections [27]. Currently identified rumen epithelial desmosome proteins include desmoglein 1 and desmocollin 1 (DSG1). Feeding dairy cows high-concentrate diets (concentrate-to-forage ra-

tio 70:30) significantly downregulated desmoglein 1 gene expression [26]. Goats fed high-concentrate diets (60:40 ratio) similarly showed reduced desmoglein 1 expression, indicating diminished rumen epithelial cell junction function under high-concentrate feeding. Subsequent SARA research feeding goats diets with NFC/NDF of 3.23 detected significantly lower desmoglein 1 expression in SARA groups versus controls, suggesting that progressive increases in dietary concentrate-to-forage ratio gradually alter rumen epithelial structure, with SARA exerting significant impacts on desmosome junctions that severely disrupt intercellular connections [14] and trigger inflammatory responses.

2.2.3 Effects on Adhesion Junctions

Adhesion junctions utilize the cytoskeletal system to create ordered, robust cell assemblies between cells and matrix or between adjacent cells, providing strong adhesive resistance to mechanical tension. These junctions are widely distributed in epithelial tissues.

Adhesion junctions primarily exist in the stratum granulosum and comprise two main types: microfilament-associated adhesion junctions including adherens junctions and focal adhesions [28], collectively termed adherens junctions. These form sheet-like transcellular networks through intracellular adhesion proteins and transmembrane adhesion proteins, integrating tissues into cohesive units. The second type includes intermediate filament-associated adhesion junctions such as desmosomes and hemidesmosomes, which participate in nutrient transport processes. The ruminant rumen undergoes continuous peristalsis under vagal control, experiencing persistent mechanical stretching that adhesion junctions must resist by maintaining plasma membrane adhesion between adjacent cells. During ruminal acidosis, adhesion junction protein gene expression downregulates, enlarging intercellular spaces, though specific regulatory mechanisms require further investigation [14].

2.2.4 Effects on Gap Junctions

Gap junctions represent the only known membrane channel structures enabling direct intercellular substance exchange [29]. These specialized channels facilitate intercellular electrical and chemical signal communication, enabling coordinated cellular responses and metabolic coupling. Gap junctions are ubiquitous in vertebrate granulosum and spinosum cell layers, forming channels that are not continuously open. Cells regulate channel opening states to control substance transport and signal transduction, thereby modulating intercellular electrochemical and metabolic coupling. Beyond their role in information and substance transfer, gap junction intercellular coupling has applications in embryonic development and tumor therapy. While 21 connexin proteins have been identified in humans and 20 in mice, only Connexin 43 has been confirmed in ruminant rumen epithelium. Studies show that increasing dietary concentrate levels in ruminants depresses ruminal pH and downregulates Connexin 43 gene expression, impairing rumen barrier function [23]. Cheng [14] validated these findings,

reporting significantly lower Connexin 43 expression in SARA groups versus controls, indicating compromised gap junction function. In vitro rumen epithelial cell culture studies represent another widely applied methodology. Wang [26] cultured primary rumen epithelial cells to examine pH and VFA effects on Connexin 43, finding that low pH significantly increased gene expression while VFAs had opposite effects. This discrepancy may arise because dual-factor in vitro studies cannot fully replicate the complex in vivo environment and metabolic state, with factors such as goat breed, rumen tissue sampling location, and experimental design potentially influencing results.

2.3 Effects of SARA on Rumen Epithelial Electrophysiology

Increased rumen epithelial permeability serves as a crucial marker of early barrier damage. Danish scholar Ussing first employed the Ussing chamber system to study epithelial ion transport [30], and this technique has become a research hotspot for investigating gastrointestinal epithelial permeability. Electrophysiological parameters in Ussing chambers reflect rumen epithelial permeability: short-circuit current (Isc) indicates ion transport capacity across epithelium, with increased Isc reflecting enhanced ion transport; tissue conductance (Gt) reflects ion permeability and primarily indicates epithelial barrier integrity, with increased Gt signifying compromised mucosal integrity and elevated permeability; transepithelial potential difference (PD) indicates tissue viability. These parameters collectively reflect epithelial barrier function [31].

Using isotopic or molecular markers to measure gastrointestinal epithelial transit ratios in Ussing chambers has become a common and important methodology [32], with common markers including horseradish peroxidase (HRP), fluorescein isothiocyanate (FITC), and ^{3}H-mannitol [33]. Through continuous application and refinement, this technique has become the "gold standard" for evaluating gastrointestinal barrier function [14].

Klevenhusen et al. [33] utilized Ussing chambers to study rumen epithelial permeability, finding that high-concentrate diets significantly increased Isc and Gt while elevating flux rates of both large-molecule marker HRP and small-molecule marker FITC, demonstrating significantly increased rumen epithelial permeability. Yang [12] investigated SARA's electrophysiological effects, reporting that SARA and recovery groups exhibited significantly higher Isc, Gt, and HRP flux rates, along with significantly lower PD values compared to controls. Our research group previously employed HRP and FITC as molecular markers, demonstrating that SARA increased Isc and Gt while decreasing PD in dairy goats both acutely and chronically, with significantly elevated HRP and FITC transit rates [34]. These findings align with Klevenhusen et al. [33] and Yang [12], confirming that SARA compromises rumen epithelial integrity, increases permeability to molecular markers, and chronically impairs barrier function.

3.2 Volatile Fatty Acids (VFA)

Rumen anaerobic microbes degrade carbohydrates into VFAs, which the rumen epithelium absorbs efficiently, primarily through passive transport, to provide 60–80% of the animal' s energy requirements. VFAs are short-chain fatty acids (C2–C6), with acetate, propionate, and butyrate comprising approximately 95% of total VFA (TVFA) [39]. Propionate serves as an effective gluconeogenic precursor supplying metabolic glucose. Ruminants secrete saliva through mastication and rumination, with high-producing cows generating approximately 79.8–90 mol/d of VFAs in the rumen. Saliva neutralizes about 30–40% of ruminal H , maintaining acid-base homeostasis [40].

Khafipour et al. [41] induced SARA with concentrate diets, observing decreased acetate concentrations and increased propionate and butyrate levels, with the acetate-to-propionate ratio declining from 3.0:1.0 to 2.1:1.0. Wu [15] induced SARA in dairy goats by progressively increasing dietary NFC/NDF ratios, finding elevated TVFA concentrations with increasing trends for acetate, propionate, and butyrate, though lactate remained consistently low throughout the trial. Costa et al. [42] similarly reported increased ruminal VFA concentrations after high-concentrate feeding. Other studies demonstrated that increasing dietary NFC/NDF decreased acetate concentration and acetate-to-propionate ratio while increasing TVFA concentrations. When NFC/NDF reached 2.58 and SARA was successfully induced, acetate concentration and acetate-to-propionate ratio decreased significantly while TVFA increased markedly, indicating close association between elevated butyrate and SARA development [43].

Weng [44] elucidated molecular-level changes in VFA absorption under high-concentrate feeding. Comparing different diets in dairy cows, feeding 62.9% concentrate with single corn straw roughage downregulated expression of VFA transporter genes sodium-hydrogen exchanger (NHE) 1, NHE3, and NHE4 in rumen papillae, while significantly upregulating monocarboxylate transporter-1 (MCT-1) and downregulating acyl-CoA synthetase short-chain family member 1 (ACSS-1) expression compared to 41.4% concentrate with mixed roughage.

3.3 Abnormal Rumen Metabolites

Endotoxin, a Gram-negative bacterial cell wall component, functions as a permeability barrier [45]. During SARA, ruminal Gram-negative bacteria lyse, releasing endotoxin into the rumen that damages epithelial cells and compromises barrier function [46]. Endotoxin subsequently translocates across the rumen barrier into circulation [47], increasing blood endotoxin concentrations and triggering systemic inflammatory responses while elevating immune activation status [48]. Accumulation to critical levels induces endotoxemia. Our previous research demonstrated that increasing dietary NFC/NDF elevated plasma endotoxin concentrations and induced endotoxemia in dairy goats [49]. Literature also reports increased endotoxin concentrations in plasma or rumen fluid

during high-concentrate induced SARA [37]. Our earlier findings showed that increasing dietary NFC/NDF from 1.40 to 3.23 progressively increased plasma endotoxin from 15.76×10^3 EU/mL to 85.55×10^3 EU/mL, consistent with previous reports [50]. Chin et al. [51] found that endotoxin increased nitric oxide (NO) production in intestinal epithelial cells, disrupting tight junction protein ZO-1 and altering its structure and function. Zhang [52] investigated dietary effects on plasma endotoxin and metabolite patterns, demonstrating that plasma endotoxin concentrations were primarily influenced by dietary concentrate-to-forage ratio, while plasma metabolites closely correlated with immune and production performance changes [53].

Histamine (HIS) is an important biologically active substance and key mediator in type I hypersensitivity reactions, participating in allergic responses, vasoconstriction/vasodilation, inflammatory reactions, and immune damage. During SARA, the disrupted ruminal environment maintains low pH conditions that promote histidine decarboxylation to form HIS, increasing abnormal metabolites [53] and damaging rumen mucosa while reducing barrier function. These abnormal metabolites, including HIS, enter circulation through the compromised rumen mucosa, triggering systemic inflammation [1]. Guo et al. [54] reported increasing blood HIS concentrations with rising dietary NFC/NDF ratios. Aschenbach et al. [25] demonstrated that HIS induces apoptosis, increases cell sloughing, and interferes with nuclear division and cell maturation, indicating that abnormal HIS metabolites disrupt epithelial regeneration during SARA, causing cellular damage and inflammatory responses. Additionally, reports indicate that when dairy cows develop SARA at NFC/NDF of 2.58, ruminal HIS concentration rises to 116.74 ng/mL, while plasma HIS shows initial elevation followed by decline [1]. Elevated HIS concentrations correlate with pathological changes, trigger inflammatory responses, and represent an important SARA pathogenic factor that exacerbates disease progression.

3.4 Rumen Microflora

The rumen harbors extensive microbial populations including fungi, bacteria, and protozoa that form a stable symbiotic fermentation system. Excessive consumption of readily fermentable carbohydrates dramatically increases microbial growth rates, accelerating fermentation and producing excessive organic acids that lower ruminal pH and induce SARA. SARA development alters microbial structure and populations: protozoa die in large numbers, fiber-degrading bacteria decrease, and Gram-negative bacteria undergo massive lysis [55]. Han et al. [56] induced SARA in dairy goats, showing that protozoal populations peaked at NFC/NDF of 1.24 but declined precipitously with increasing NFC/NDF, reaching minimum values during SARA. Guo et al. [54] similarly found that starch-degrading bacteria showed the most pronounced changes during SARA, increasing with NFC/NDF elevation. As ruminal pH further declines, microbial balance is disrupted, acid-tolerant bacteria proliferate, and harmful substances like lactate accumulate, aggravating SARA. Simultaneously, *Fusobac-*

terium necrophorum populations surge to more than ten times normal levels. *Prevotella ruminicola* exhibits broad pH buffering capacity, and while most fiber-degrading bacteria lose activity at pH 6.0, genetically engineered *P. ruminicola* B.4 strains can survive pH 5.5 environments, making genetic regulation of acid-resistant fiber-degrading bacteria one of the most effective approaches for rumen microbial manipulation [40].

3.5 Other Factors

SARA exerts insidious effects on ruminant health, disrupting immune function by promoting cell-mediated immunity and increasing inflammatory cell secretion. Reduced feed intake and milk yield cause severe economic losses. Progressive SARA development leads to diarrhea, intestinal mucosal damage, laminitis, liver abscesses, and other inflammatory conditions [57].

4 Conclusion

SARA development not only alters rumen epithelial structure and function but also disrupts ruminal fermentation, modifies microbial community structure, and increases abnormal metabolites, thereby compromising rumen mucosal integrity and damaging epithelial barrier structure. While most research has focused on SARA prevention, diagnosis, treatment, and pathology, the precise mechanisms and pathways of rumen epithelial damage remain unclear. Therefore, in-depth investigation of SARA' s effects on rumen epithelial barrier function and molecular regulatory mechanisms is necessary. Concurrently, the era of big data has generated numerous sequencing analyses, with rumen microbial metagenomics emerging as a promising field. This approach will guide understanding of SARA-associated functional gene regulatory networks and microecological environments, identify key signaling pathways, and provide theoretical foundations for developing nutritional strategies that improve feed efficiency and maintain rumen health under high-concentrate feeding conditions.

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Note: Figure translations are in progress. See original paper for figures.