Effects of Subacute Ruminal Acidosis on Abnormal Plasma Metabolites and Biochemical Indices in Dairy Goats (Postprint)

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Abstract

This study induced subacute ruminal acidosis (SARA) in dairy goats by gradually increasing the dietary non-fibrous carbohydrate to neutral detergent fiber ratio (NFC/NDF), aiming to investigate changes in plasma histamine (HIS), lipopolysaccharide (LPS) concentrations, and biochemical parameters during SARA induction. Four healthy lactating Saanen dairy goats with similar body weight were selected and sequentially fed four diets with NFC/NDF ratios of 1.40, 1.79, 2.31, and 3.23. Each diet was fed for 15 days (as one group), with the first 12 days as an adaptation period and the last 3 days as a sampling period. Plasma HIS and LPS concentrations were determined by enzyme-linked immunosorbent assay (ELISA), and plasma biochemical parameters were measured using a biochemical analyzer. The results showed: 1) When dietary NFC/NDF increased from 1.40 to 3.23, SARA was successfully induced in dairy goats. 2) During SARA induction, plasma HIS and LPS concentrations increased with increasing dietary NFC/NDF, and were significantly higher at NFC/NDF of 3.23 than at NFC/NDF of 1.40 ($P<0.05$). 3) With increasing dietary NFC/NDF, plasma immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin G (IgG) concentrations showed no significant changes ($P>0.05$); plasma creatinine (CREA), D-lactate (LD) concentrations, and activities of creatine kinase (CK), aspartate aminotransferase (AST), and diamine oxidase (DAO) showed no significant changes ($P>0.05$); plasma gamma-glutamyl transferase (γ-GT) activity showed an increasing trend, being significantly higher at NFC/NDF of 3.23 than in other groups ($P<0.05$); plasma urea nitrogen (UN) concentration decreased, being significantly higher at NFC/NDF of 1.40 than in other groups ($P<0.05$); plasma alkaline phosphatase (ALP) activity increased, being extremely significantly higher at NFC/NDF of 3.23 than in the other three groups ($P<0.01$); plasma free fatty acid (FFA) concentration first increased and then decreased, being extremely significantly higher at NFC/NDF of 2.31

than in other groups (P<0.01); plasma β-hydroxybutyrate (β-HB) concentration decreased, being extremely significantly higher at NFC/NDF of 1.40 than in other groups (P<0.01). These results suggest that with increasing dietary NFC/NDF, plasma HIS and LPS concentrations increased significantly, triggering systemic inflammatory responses, aggravating rumen epithelial damage and SARA severity, and activating the immune status of dairy goats; during SARA induction, plasma biochemical parameters changed to varying degrees, indicating that dairy goats were in a stress state during SARA, which induced hepatic function damage.

Full Text

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Abstract

This study investigated changes in plasma histamine (HIS), lipopolysaccharide (LPS) content, and biochemical indices in dairy goats during subacute ruminal acidosis (SARA) induction through incremental increases in dietary non-fiber carbohydrate to neutral detergent fiber ratio (NFC/NDF). Four healthy lactating Saanen dairy goats with similar body weight were sequentially fed four diets with NFC/NDF ratios of 1.40, 1.79, 2.31, and 3.23. Each diet was fed for 15 days (constituting one group), with the first 12 days as an adaptation period and the last 3 days as a sampling period. Plasma HIS and LPS contents were measured by enzyme-linked immunosorbent assay (ELISA), while biochemical indices were determined using a biochemical analyzer. The results demonstrated: (1) SARA was successfully induced when dietary NFC/NDF increased from 1.40 to 3.23. (2) During SARA induction, plasma HIS and LPS contents increased with rising dietary NFC/NDF, with significant differences observed between the 3.23 and 1.40 NFC/NDF groups (P<0.05). (3) With increasing dietary NFC/NDF, plasma immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin G (IgG) contents showed no significant changes (P>0.05). Similarly, plasma creatinine (CREA), D-lactate (LD) contents, and activities of creatine kinase (CK), aspartate aminotransferase (AST), and diamine oxidase (DAO) remained unchanged (P>0.05). However, plasma γ-glutamyl transferase (γ-GT) activity exhibited an increasing trend, with the 3.23 NFC/NDF group significantly higher than other groups (P<0.05). Plasma urea nitrogen (UN) content decreased, with the 1.40 NFC/NDF group significantly higher than others (P<0.05). Plasma alkaline phosphatase (ALP) activity increased, with the 3.23 NFC/NDF group extremely significantly higher than the other three

groups (P<0.01). Plasma free fatty acid (FFA) content first increased then decreased, being extremely significantly higher in the 2.31 NFC/NDF group compared to others (P<0.01). Plasma β-hydroxybutyric acid (β-HB) content decreased, with the 1.40 NFC/NDF group extremely significantly higher than other groups (P<0.01). These findings indicate that incremental increases in dietary NFC/NDF significantly elevate plasma HIS and LPS contents, triggering inflammatory responses, aggravating rumen epithelial damage and SARA severity, and activating immune status. The observed changes in plasma biochemical indices suggest that dairy goats experience stress during SARA, resulting in hepatic function impairment.

Keywords: subacute ruminal acidosis; biochemical indices; dairy goats; nonfiber carbohydrate/neutral detergent fiber ratio; lipopolysaccharide; histamine

Introduction

Subacute ruminal acidosis (SARA), also known as chronic or subclinical ruminal acidosis, represents one of the most common nutritional metabolic diseases in modern ruminant production, particularly prevalent in intensive beef cattle fattening and high-yielding dairy operations. This condition severely compromises long-term animal health and production efficiency, warranting substantial research attention. Epidemiological surveys indicate that 19% of early-lactation and 26% of mid-lactation dairy cows in the United States suffer from SARA [2-3]. Previous studies have demonstrated that SARA induction in goats generates substantial lipopolysaccharide (LPS) in the rumen, which subsequently translocates into the bloodstream [4-6]. Circulating LPS then triggers systemic production of cytokines and acute-phase proteins. Although no universal diagnostic criteria for SARA have been established, most researchers adopt ruminal fluid pH as the primary indicator, with pH $\leq$ 5.5 serving as the standard threshold [7-8]. SARA inflicts continuous damage through various toxic substances, with research showing that plasma LPS content progressively increases during SARA episodes, initiating systemic inflammatory responses. Guo et al. [9] reported that plasma histamine (HIS) content peaked at 22.28 ng/mL when dietary NFC/NDF reached 1.63. Other studies documented HIS concentrations of 3-70 mg/L in dairy cows with SARA when ruminal pH declined to 4.5 [10]. However, Lachmann et al. [11] found no significant changes in blood parameters during SARA episodes. Zhang [12] investigated the effects of different dietary patterns on plasma LPS and metabolite profiles, concluding that plasma LPS content was primarily influenced by dietary concentrate-to-forage ratio, while plasma metabolites correlated closely with immune changes and growth performance. Nevertheless, research on plasma metabolite alterations and biochemical indices in ruminants with SARA remains insufficient. This study employed a gradual NFC/NDF increment protocol to induce SARA in dairy goats, which aligns with natural feeding patterns [13]. A continuous pH monitoring system was used to assess ruminal fluid pH, with SARA diagnosed when pH remained below 5.6 for more than 3 hours within a 24-hour period [14]. This approach

enabled examination of the relationship between dietary NFC/NDF ratios and plasma HIS, LPS, and biochemical indices, providing theoretical insights into SARA pathophysiology.

Materials and Methods

Experimental Animals and Management

Four healthy lactating Saanen dairy goats (2-3 years old, body weight 43.58 ± 2.77 kg) fitted with permanent rumen fistulas were selected for the study conducted from September 2015 to January 2016 at the Animal Experimental Base of Inner Mongolia Academy of Animal Sciences. Animals were housed individually and fed twice daily with equal portions, receiving roughage before concentrate, with ad libitum access to water.

Experimental Diets

Diets were formulated according to NRC (1989) [15] and Jin' s recommended feeding standards for dairy goats [16], using corn, soybean meal, wheat bran, alfalfa, and green hay as primary ingredients to create four diets with NFC/NDF ratios of 1.40, 1.79, 2.31, and 3.23. Diet composition and nutrient levels are presented in Table 1 .

Experimental Design

A self-controlled trial design was employed to induce SARA through stepwise increases in dietary NFC/NDF. The experiment comprised four periods of 15 days each, corresponding to diets with NFC/NDF ratios of 1.40 (Period I), 1.79 (Period II), 2.31 (Period III), and 3.23 (Period IV). Each period served as one experimental group, with the first 12 days as a preliminary period and the last 3 days as a sampling period. A continuous pH monitoring system recorded ruminal fluid pH for 24 hours to evaluate SARA induction. Based on Ramanzin et al. [17] and Penner et al. [18], SARA was considered successfully induced when ruminal pH remained between 5.5-5.2 for more than 3 hours within 24 hours.

Main Instruments

The study utilized a microplate reader (Awareness, USA), semi-automatic biochemical analyzer (A6, Beijing Songshang Technology Co., Ltd.), pH electrode (S651CD, Sensorex, USA), transmitter (692, Jenco, USA), paperless recorder (R4100, Zhejiang Zhongkong Instrument Co., Ltd.), and automatic biochemical analyzer (BS-420, Mindray, China).

Sample Collection and Analysis

Rumen Fluid pH Monitoring A continuous pH monitoring system was employed to dynamically record ruminal fluid pH during sampling periods. The

system consisted of a pH electrode (inserted into the rumen), pH transmitter, and paperless recorder configured to display data every 5 seconds and record every 10 minutes. Data were uploaded to a computer for analysis of mean, maximum, and minimum pH values, duration of pH < 5.5, and curve area (calculated as the sum of absolute deviations from the pH threshold multiplied by time interval).

Plasma Collection and Processing During each sampling period, 20 mL of blood was collected from the jugular vein before morning feeding, centrifuged at 3,500 r/min for 10 minutes, and plasma was harvested and stored at -20°C in 2 mL tubes.

Plasma LPS, HIS, and Biochemical Indices Determination HIS content was measured using a kit from DiaSource (USA) according to manufacturer instructions. LPS content was determined using a kit from Nanjing Jiancheng Bioengineering Institute following the provided protocol. Semi-automatic biochemical analyzer was used to measure creatinine (CREA), D-lactate (LD), β-hydroxybutyric acid (β-HB), free fatty acids (FFA), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), and diamine oxidase (DAO) activity. Automatic biochemical analyzer determined aspartate aminotransferase (AST), γ-glutamyl transferase (γ-GT), creatine kinase (CK), alkaline phosphatase (ALP) activities, and urea nitrogen (UN) content.

Statistical Analysis

All data were organized in Excel and analyzed using one-way ANOVA in SAS 9.0 software. Duncan's multiple range test was applied for post-hoc comparisons. Results are expressed as mean $\pm$ standard deviation, with $P < 0.05$ considered significant and $P < 0.01$ considered extremely significant.

Results

Effects of Different NFC/NDF Diets on Rumen Fluid pH

Table 2 shows substantial changes in ruminal fluid pH during SARA induction. When NFC/NDF increased from 1.40 to 1.79 and 2.31, mean and minimum pH values were significantly lower than in the 1.40 group ($P < 0.05$) but significantly higher than in the 3.23 group ($P < 0.05$). The 1.40 group exhibited significantly lower maximum pH compared to the other three groups ($P < 0.05$). Overall, increasing dietary NFC/NDF resulted in declining maximum, minimum, and mean pH values, while the curve area for pH < 5.5 and pH < 5.8 showed an upward trend. These findings demonstrate that ruminal fluid pH underwent significant changes during SARA induction in dairy goats.

Effects of Different NFC/NDF Diets on Plasma LPS and HIS Contents

As shown in Table 3 , plasma LPS and HIS contents increased progressively with rising dietary NFC/NDF during SARA induction, reaching maximum values in the 3.23 NFC/NDF group. LPS content was significantly higher in the 2.31 and 3.23 groups compared to the 1.40 group ($P < 0.05$), though differences with the 1.79 group were not significant ($P > 0.05$). HIS content in the 3.23 group was significantly higher than in the other three groups ($P < 0.05$), with no significant differences among the remaining groups ($P > 0.05$).

Effects of Different NFC/NDF Diets on Plasma Biochemical Indices

Different NFC/NDF diets exerted varying effects on plasma biochemical indices in dairy goats. Regarding immunoglobulin contents (Table 4), IgA content was highest in the 2.31 NFC/NDF group, IgG content peaked in the 3.23 group, and IgM content was highest in the 2.31 group, though none of these differences reached statistical significance ($P > 0.05$).

As presented in Table 5 , AST activity showed no significant differences among groups ($P > 0.05$). γ-GT activity was significantly higher in the 3.23 NFC/NDF group compared to other groups ($P < 0.05$). CREA content did not differ significantly among groups ($P > 0.05$). UN content was significantly higher in the 1.40 group than in other groups ($P < 0.05$), while no significant differences existed among the 1.79, 2.31, and 3.23 groups ($P > 0.05$). CK activity remained unchanged across groups ($P > 0.05$). ALP activity was extremely significantly higher in the 3.23 group compared to the other three groups ($P < 0.01$), with no significant differences among the latter ($P > 0.05$). LD content showed no significant variation among groups ($P > 0.05$). FFA content was extremely significantly higher in the 2.31 group than in the other three groups ($P < 0.01$), with no significant differences among the remaining groups ($P > 0.05$). DAO activity did not differ significantly among groups ($P > 0.05$). β-HB content was extremely significantly higher in the 1.40 group compared to the other three groups ($P < 0.01$), with no significant differences among the latter ($P > 0.05$).

Discussion

Effects of Different NFC/NDF Diets on Plasma Abnormal Metabolites

LPS, a component of Gram-negative bacterial cell walls, functions as a permeability barrier [19]. During SARA episodes, massive bacterial LPS release from ruminal Gram-negative bacteria disrupts ruminal barrier function and damages rumen epithelial cells [20], subsequently translocating into the bloodstream [21] and increasing circulating LPS content, which triggers systemic inflammatory responses and activates immune status [22]. Accumulation of LPS to certain levels induces endotoxemia. Previous reports indicate that increasing dietary

NFC/NDF elevates plasma LPS content and induces endotoxemia in dairy goats [19,23], with high-grain diets inducing SARA in ruminants often accompanied by increased plasma LPS [24]. In this study, plasma LPS content increased significantly from 15.76×10^3 EU/mL to 85.55×10^3 EU/mL as NFC/NDF rose from 1.40 to 3.23, consistent with previous findings. These results demonstrate that varying dietary NFC/NDF affects immune activation status and continuously triggers inflammatory responses in goats.

Histamine is a crucial biologically active substance and a key mediator in type I hypersensitivity reactions, participating in allergic responses, vasoconstriction and dilation, and serving as an important inflammatory and immune damage mediator. During SARA, ruminal environment disruption and prolonged low pH conditions promote histidine decarboxylation to form HIS, increasing abnormal metabolites [25] and causing rumen mucosal damage that compromises ruminal barrier function. Abnormal metabolites like HIS readily enter the bloodstream through damaged rumen mucosa, eliciting inflammatory reactions [26]. This study found that plasma HIS content increased progressively with NFC/NDF, peaking at 1.04 ng/mL in the 3.23 group, aligning with Guo et al. [9]. Aschenbach et al. [27] reported that HIS induces apoptosis, increases cell shedding, or interferes with nuclear division and cell maturation, suggesting that HIS may impair epithelial cell regeneration during SARA, thereby causing cellular damage and inflammatory responses. Although HIS concentrations of 3-70 mg/L have been reported in SARA-affected dairy cows with pH declining to 4.5 [9], this study detected lower values likely due to methodological differences, though the trend was consistent with previous research. Nagaraja et al. [29] noted that SARA causes rumen epithelial cell parakeratosis and inflammation. Therefore, elevated plasma HIS content in dairy goats correlates with pathological changes and may constitute an important factor aggravating SARA progression.

Effects of Different NFC/NDF Diets on Plasma Immunoglobulin Contents

Immune stimulation triggers immunoglobulin production; while appropriate stimulation enhances immune function, excessive stimulation increases energy expenditure and compromises production performance. Blood proteins maintain homeostasis, with IgA, IgG, and IgM representing major immunoglobulins that may respond differently to environmental stimuli. In this study, various immunoglobulins showed non-significant increases at NFC/NDF ratios of 2.31 and 3.23, possibly because gradual SARA formation produced stimulatory effects that triggered homeostatic responses, reducing protein redistribution and decreasing immune activation status [30].

Effects of Different NFC/NDF Diets on Plasma Biochemical Indices

Under normal conditions, plasma ALP originates primarily from bone, where osteoblasts produce it for excretion via the hepatobiliary system. ALP activity closely correlates with blood calcium metabolism, with decreased calcium indi-

cating elevated ALP. In this study, ALP activity was significantly higher in the 3.23 NFC/NDF group, likely because increased dietary NFC/NDF elevated energy supply and milk production, enhancing calcium mobilization and turnover. This suggests calcium deficiency during SARA pathogenesis and indicates hepatobiliary system involvement.

AST is an important transaminase and a clinical indicator of hepatic function used to assess liver damage, with significant elevation occurring during severe hepatic injury [31]. Normal plasma AST activity in adult dairy cows ranges from 12.9-104.0 U/L [32]. In this study, AST activity exceeded normal limits in the 3.23 group, while remaining slightly elevated within normal ranges for the other three diets, indicating progressive liver damage with increasing NFC/NDF. Plasma γ-GT originates mainly from the liver, with elevated activity signaling active hepatic injury. The significant increase in γ-GT activity observed in the 3.23 group suggests severe hepatic dysfunction induced by SARA.

Blood CREA and UN serve as indicators of protein metabolism and renal function in ruminants. UN content is influenced by ruminal fermentation capacity, dietary amino acid composition, hepatic and renal function, and carbohydrate and protein intake [33], reflecting glomerular filtration and protein metabolism status while indicating water-electrolyte balance. CREA, formed from creatine dehydration and excreted in urine, can be filtered through glomeruli with minimal tubular reabsorption. Under normal conditions, CREA is metabolized and eliminated, but renal dysfunction causes accumulation and toxicity. This study showed that decreasing ruminal pH during SARA increased plasma CREA content while significantly reducing UN from 8.16 mmol/L to 5.72 mmol/L, contrasting with Wang et al. [34] who reported significantly elevated UN in SARA-affected cattle. These findings suggest possible dehydration or renal function impairment during SARA, potentially related to altered protein metabolism. Increased protein catabolism enhances hepatic amino acid metabolism, converting to urea and forming UN. The significantly lower UN content in the 2.31 and 3.23 groups compared to the 1.40 group indicates reduced protein turnover in SARA-affected goats, demonstrating severe hepatic dysfunction with increasing NFC/NDF.

β-HB, the primary ketone body component, serves as a diagnostic indicator for ketosis. Li et al. [35] confirmed that subclinical ketosis is characterized by blood β-HB content of 1.2 mmol/L. In this study, plasma β-HB remained within normal ranges, suggesting no ketosis risk during SARA episodes. FFA, a major milk fat component [36], is selectively taken up by mammary glands from blood, with precursor interactions affecting milk fat synthesis and quality [37]. The extremely significant increase in plasma FFA content in the 2.31 group suggests maximal FFA synthesis and elevated milk fat at this NFC/NDF ratio, consistent with Zhang [38] who reported higher plasma glycerol and FFA in high-concentrate fed lactating goats.

DAO, an intracellular enzyme in mammalian small intestinal mucosal villous epithelial cells, normally exhibits low plasma activity, making it an accurate

indicator of intestinal mucosal structure and function. Mucosal damage and compromised barrier function release substantial DAO from villous epithelial cells into circulation [39]. The progressive increase in plasma DAO content with rising NFC/NDF indicates gradual rumen epithelial damage. CK, a sensitive stress indicator involved in ATP synthesis for energy supply, increases with animal stimulation [40]. LD, another stress marker present in liver, heart, and muscle, elevates when these organs are damaged. As a metabolic end-product of gastrointestinal bacteria that mammals cannot synthesize or metabolize, increased LD in blood indicates enhanced gastrointestinal permeability [41-42]. Simaraks et al. [43] reported negative correlation between blood LD and stress resistance. CK activity also serves as a hepatic function indicator [40]. This study found non-significantly higher LD content in the 2.31 group and non-significantly elevated DAO activity in the 3.23 group, while CK activity remained high except for a slight decrease in the 2.31 group, suggesting weakest stress resistance and increased mucosal permeability at NFC/NDF 2.31. Wang [44] reported significantly elevated biochemical indices in SARA-affected beef cattle compared to healthy controls, indicating inflammatory responses. Collectively, these results demonstrate that progressive NFC/NDF increase gradually damages rumen epithelium and impairs hepatic and renal function in goats.

Conclusions

Incremental increases in dietary NFC/NDF significantly elevate plasma LPS and HIS contents, triggering inflammatory responses that aggravate rumen epithelial damage and SARA severity while activating immune status in dairy goats. During SARA induction through dietary NFC/NDF elevation, plasma biochemical indices exhibit varying changes, indicating that dairy goats experience stress during SARA episodes, which induces hepatic function impairment.

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