Absorption and Metabolism of Short-Chain Fatty Acids in Rumen Epithelium: Postprint

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Abstract

Short-chain fatty acids are important products of rumen fermentation in ruminants, primarily consisting of acetate, propionate, and butyrate, which are mainly absorbed through the rumen epithelium. Propionate undergoes gluconeogenesis in the liver to produce glucose, providing energy for the organism. With in-depth research on short-chain fatty acids, it has been discovered that their absorption across the rumen epithelium occurs via passive diffusion and specific carrier-mediated transport. Related transporters include monocarboxylate transporters (MCT), Na+/H+ exchangers (NHE), and anion exchanger 2 (AE2), among others. The transport and absorption of short-chain fatty acids across the rumen epithelium are also related to the pH of the rumen lumen and intracellular pH, with interactions among these transporters collectively maintaining pH homeostasis in the rumen lumen and within cells. After being absorbed into cells, short-chain fatty acids undergo intracellular metabolism, with the main metabolic pathways including cholesterol synthesis and ketone body synthesis pathways. Ketone body synthesis occurs in mitochondria, while cholesterol synthesis takes place in the cytoplasm and endoplasmic reticulum, and the precursor for both pathways is 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). The synthesized ketone bodies are transported out of epithelial cells by MCT and enter peripheral tissues to provide energy. This article reviews the absorption and metabolic regulatory mechanisms of short-chain fatty acids in the rumen epithelium, providing a theoretical basis for future research.

Full Text

Absorption and Metabolism of Short Chain Fatty Acids in Ruminal Epithelium

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Abstract

Short-chain fatty acids (SCFAs) are important products of rumen fermentation in ruminants, primarily consisting of acetate, propionate, and butyrate. These SCFAs are mainly absorbed through the ruminal epithelium, with propionate undergoing gluconeogenesis in the liver to supply glucose and energy to the body. Recent research has revealed that SCFA absorption across the ruminal epithelium occurs via both passive diffusion and specific carrier-mediated transport. Key transporters include monocarboxylate transporters (MCT), Na+/H+ exchangers (NHE), and anion exchanger 2 (AE2). The transport and absorption of SCFAs are closely associated with pH regulation in both the rumen lumen and intracellular compartments, with various transporters working in concert to maintain pH homeostasis. Following absorption, SCFAs undergo active metabolism within epithelial cells, with metabolic rates exceeding 50% —butyrate showing the highest metabolic rate. The primary metabolic pathways are ketone body synthesis and cholesterol synthesis, both of which share 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) as a common precursor. Ketone body synthesis occurs in mitochondria, while cholesterol synthesis takes place in the cytoplasm and endoplasmic reticulum. The synthesized ketone bodies are exported from epithelial cells via MCTs to peripheral tissues for energy utilization; however, excessive ketogenesis can lead to elevated blood ketone concentrations and potentially cause ketosis. Conversely, excessive cholesterol accumulation can trigger cellular inflammation and oxidative stress, compromising energy supply and overall health. Therefore, understanding SCFA transport and absorption mechanisms in the ruminal epithelium is crucial for elucidating rumen dynamics and developing nutritional regulation strategies.

Keywords: ruminal epithelium; short-chain fatty acid; absorption; metabolism

1. Ruminal Epithelial Morphology and Function

The ruminal epithelium performs essential physiological functions including SCFA absorption, metabolism, and rumen protection. It possesses a stratified structure comprising four distinct layers from the luminal surface inward: the stratum corneum, granular layer, spinous layer, and basal layer. Basal layer cells are rich in mitochondria, while spinous layer cells contain fewer mitochondria. The granular and spinous layers represent the primary sites of SCFA metabolism. Cells in the granular layer are tightly connected via gap junctions, and the outermost stratum corneum consists of highly keratinized cells that serve as a protective barrier against the physical environment of the rumen. The thickness of the stratum corneum is regulated by SCFA concentrations; when dietary concentrate-to-forage ratio increases, the propionate/acetate ratio rises, SCFA concentrations increase, and rumen pH decreases, causing the stratum corneum to expand from 4 to as many as 15 cell layers.

Ruminal papillae, which are leaf-like structures covering the epithelium, signif-

icantly increase the surface area for SCFA absorption, with papillae in cattle reaching 10–15 mm in length. As the primary structures for nutrient absorption, papillae density and size directly influence SCFA uptake. Research indicates that high-protein and high-energy diets elevate insulin-like growth factor 1 (IGF-1) concentrations, which activate the downstream Ras/Raf/MEK/ERK signaling pathway upon receptor binding, upregulate cyclin D1 expression, and promote ruminal epithelial cell proliferation, thereby enhancing SCFA absorption. Additionally, Yazdi et al. demonstrated that heat stress can increase papillae height. These findings illustrate that ruminal epithelial morphology and SCFA absorption exist in a dynamic equilibrium, coordinating to maintain rumen homeostasis.

2. SCFA Absorption Across Ruminal Epithelium

Although concentration gradients exist between the rumen lumen and intracellular compartments, SCFA absorption is not simply a matter of passive diffusion along these gradients. SCFAs exist in both dissociated and undissociated forms within the rumen lumen, predominantly as undissociated acids, resulting in distinct transport mechanisms. In vitro studies have shown that butyrate exhibits the highest net absorption rate even without a concentration gradient, while acetate and propionate show lower net absorption rates. Both passive diffusion and specific carrier-mediated transport contribute to SCFA absorption.

The Na+/H+ exchanger (NHE) represents a critical membrane transport system. Undissociated SCFAs entering cells via passive diffusion release H+, causing cytoplasmic acidification that upregulates NHE expression and enhances Na+ uptake while extruding H+ into the rumen lumen. This functional coupling between SCFA-induced cytoplasmic acidification and NHE activity is essential for pH regulation. The NHE family in bovine ruminal epithelium includes NHE1, NHE2, NHE3, and NHE8, while NHE1 and NHE3 are found in goats and sheep. NHE1 maintains extracellular pH near the granular layer, as NHE1 knockout animals exhibit abnormally low local extracellular pH, highlighting its crucial role in rumen pH homeostasis.

Monocarboxylate transporters (MCT) specifically mediate the transport of SCFAs, ketone bodies, and lactate across the ruminal epithelium. Bovine ruminal epithelium expresses MCT1 and MCT2, with immunofluorescence localization placing MCT1 in the basal layer, where it cotransports dissociated SCFAs, lactate, and ketone bodies into the bloodstream, thereby removing H+ and preventing cytoplasmic acidification from excessive metabolite accumulation.

Dissociated SCFAs are transported via anion exchanger 2 (AE2), downregulated in adenoma (DRA), and putative anion 1 (PAT1), with this transport depending on HCO3- availability. Bicarbonate serves as a critical buffer for rumen digesta, originating primarily from salivary secretion and, more significantly, from transporter-mediated export by ruminal epithelial cells. Bilk et al. proposed that DRA and PAT1 neutralize acid by exporting bicarbonate

from epithelial cells while importing dissociated SCFAs. AE2 maintains intracellular pH homeostasis in ruminal epithelial cells, becoming activated when intracellular pH rises to export HCO3- and stabilize cellular pH. While the function and localization of DRA, PAT1, and AE2 have been extensively studied in intestinal cells, their specific distribution across ruminal epithelial layers remains unclear (Table 1). However, based on the role of HCO3-/H+ transporters, these carriers are likely located primarily in the granular layer due to its proximity to the rumen lumen, with possible minor distribution in the spinous and basal layers where metabolism occurs and metabolites like lactate and pyruvate could cause cytoplasmic acidification.

Table 1 Transporters of SCFA in rumen epithelium

Transporter	Isoforms	Location	Function	Method	Reference
Monocarboxylate transporter (MCT)	MCT1, MCT2	Spinous layer, basal layer	Export lactate, ketone bodies	Section preparation, incubation with primary and secondary antibodies at 4°C, fluorescence localization	[23-24]

Transporter	Isoforms	Location	Function	Method	Reference
Na+/H+ exchanger (NHE)	NHE1, NHE2, NHE3, NHE8	Granular layer, spinous layer, basal layer	Import Na+, export H+	Section preparation, incubation with primary and secondary antibodies at 4°C, fluorescence localization	[19-21]
Anion exchanger (AE)	AE2	-	Export HCO3-	RNA extraction, real-time quantitative PCR, product analysis on 1% agarose gel	[30]
Down-regulated in adenoma (DRA)	DRA	-	Export HCO3-	RNA extraction, real-time quantitative PCR, product analysis on 1% agarose gel	[29]

Transporter	Isoforms	Location	Function	Method	Reference
Putative anion transporter (PAT)	PAT1	-	Export HCO3-	RNA extraction, real-time quantitative PCR, product analysis on 1% agarose gel	[26]
Na+-HCO3- cotransporter (NBC)	NBC	-	Import Na+, export HCO3-	RNA extraction, real-time quantitative PCR, product analysis on 1% agarose gel	[33]

3. SCFA Metabolism in Ruminal Epithelial Cells

Ruminal epithelial cells exhibit high metabolic activity, with studies showing that approximately 75% of propionate and 95% of butyrate are metabolized within these cells before reaching the bloodstream. Rather than relying on glucose, ketone bodies, or glutamine for energy, ruminal epithelium primarily oxidizes SCFAs—the terminal fermentation products—to meet its energy demands, with butyrate serving as the principal metabolic substrate due to its highest metabolic rate.

Following uptake, SCFA metabolism begins with the conversion to acyl-CoA esters by the acyl-CoA synthetase family. Subsequently, 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS) converts acetyl-CoA to HMG-CoA, a central metabolite that serves as the precursor for both ketone body and cholesterol synthesis. HMG-CoA is distributed in both mitochondria and cytoplasm. HMGCS exists as two isoforms: HMGCS1 in the cytoplasm and HMGCS2 exclusively in mitochondria. HMGCS2 acts as the rate-limiting enzyme regulating ketone body synthesis in ruminal epithelial cells. De Rosa et al. found that docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA),

and arachidonic acid (AA) at concentrations of 25 and 50 μmol/L upregulated HMGCS2 expression at both transcriptional and translational levels, whereas treatment with 25 mmol/L fructose and insulin for 24 hours decreased mRNA and protein expression in human hepatoma (HepG2) cells.

Polyunsaturated fatty acids (PUFAs) regulate various metabolic pathways including de novo lipogenesis and fatty acid oxidation through binding to peroxisome proliferator-activated receptor (PPAR). The HMGCS2 promoter region contains peroxisome proliferator response elements (PPRE) that initiate HMGCS2 transcription upon PPAR binding. Studies have shown that increased PPAR mRNA expression correlates with elevated HMGCS2 mRNA levels, suggesting that PUFAs may regulate ketone body synthesis by directly binding to nuclear receptors like PPAR to upregulate HMGCS2 expression. The primary sites of ketogenesis in ruminants are the rumen and liver, with the mitochondrial ketone body synthesis pathway illustrated in Figure 1. Excessive ketogenesis in ruminal epithelium due to disordered SCFA metabolism can lead to hyperketonemia and ketosis, severely compromising animal health, making it crucial to further investigate the regulatory mechanisms of ketone body synthesis for ketosis prevention.

In addition to serving as ketone body precursors, SCFAs also undergo cholesterol biosynthesis in the cytoplasm and endoplasmic reticulum. The initial phase occurs in the cytoplasm where SCFAs are converted to HMG-CoA, which then translocates to the endoplasmic reticulum where HMG-CoA reductase (HMGR) resides. HMGR catalyzes the conversion of HMG-CoA to mevalonate (the mevalonate pathway) and represents the rate-limiting enzyme in cholesterol biosynthesis—one of the most highly regulated enzymes in nature. Mevalonate is subsequently decarboxylated to isoprenoid intermediates such as farnesyl pyrophosphate (FPP), which modulate cell proliferation, migration, and oxidative stress through membrane-associated signaling protein attachment and subcellular trafficking. The final branch point involves squalene synthase (FDPS) catalyzing FPP conversion to squalene, which is further metabolized to lanosterol and ultimately cholesterol. While cholesterol is a major mammalian cell membrane component, excessive accumulation of cholesterol and its metabolites (isoprenoids) increases membrane permeability and triggers inflammatory responses. High-concentrate diets enhance ruminal epithelial permeability and inflammation by promoting fermentation, increasing SCFA concentrations, and stimulating cholesterol biosynthesis. Steele et al. observed that feeding a high-concentrate diet for one week significantly increased ruminal SCFA concentrations, induced ruminal acidosis, and upregulated mRNA expression of cholesterol synthesis genes (HMGS1, HMGR), elevating cholesterol levels and triggering inflammation. However, after three weeks, despite persistently elevated SCFA concentrations, HMGS1 and HMGR mRNA expression decreased significantly, suppressing cholesterol synthesis and mitigating acidosis. Thus, cholesterol synthesis in ruminal epithelium is regulated by both SCFA concentration and exposure duration. Short-term SCFA elevation promotes cholesterol synthesis and increases permeability, whereas prolonged exposure activates the sterol

regulatory element binding protein (SREBP) pathway to suppress cholesterol synthesis enzymes, thereby reducing inflammation and acidosis. SREBPs are transcription factors that regulate cholesterol and lipid gene expression in bovine liver and mammary gland, with three isoforms encoded in the bovine genome: SREBP-1a, SREBP-1c, and SREBP-2, the latter preferentially activating cholesterol biosynthesis. High cholesterol concentrations promote binding of SREBP to SREBP cleavage-activating protein (SCAP) in the endoplasmic reticulum, transcriptionally suppressing cholesterol synthesis genes (Figure 2). Conversely, low cholesterol concentrations trigger SREBP-SCAP complex translocation to the Golgi apparatus, where proteolytic cleavage releases the N-terminal domain to activate nuclear gene expression and enhance cholesterol synthesis. Further investigation into the molecular regulatory mechanisms of SCFA-driven cholesterol synthesis in ruminal epithelium is essential for developing strategies to prevent and alleviate ruminal acidosis by maintaining intracellular cholesterol homeostasis and reducing inflammation.

4. Summary and Outlook

Due to the unique fermentation characteristics of the ruminant rumen, SCFAs serve as the primary energy substrate, making their absorption and metabolism in the ruminal epithelium critical for systemic energy metabolism and animal health. Elucidating these mechanisms is fundamental for nutritional regulation of rumen health. While numerous studies have characterized the various specific carrier proteins in ruminal epithelial cells, the interactions between different transporters and their responses to physiological challenges such as heat stress and ruminal acidosis remain poorly understood. Future research should integrate SCFA metabolism in ruminal epithelium with hepatic metabolism and systemic circulation to comprehensively clarify the regulatory mechanisms governing SCFA absorption and metabolism.

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