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*Review*

# Volatile fatty acids production in ruminants and the role of monocarboxylate transporters: A review

**Aluwong, Tagang[1]*, Kobo, Patricia Ishaku[2] and Abdullahi, Abdullahi[3]**

Department of Veterinary Physiology and Pharmacology, Ahmadu Bello University, Zaria, Nigeria.

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**Monocarboxylates commonly referred to as short-chain fatty acids (SCFAs) are metabolized to different extents by the epithelium of the gastrointestinal tract. They are absorbed along different segments of the gastrointestinal tract and constitute a significant amount of energy in ruminants. Monocarboxylates play a central role in cellular metabolism and metabolic communication between tissues. Essential to these roles is their rapid transport across the plasma membrane, which is catalyzed by a recently identified family of proton-linked monocarboxylate transporters (MCTs). Monocarboxylate transporter-1 and 4 have been shown to interact specifically with OX-47 (CD147), a member of the immunoglobulin superfamily with a single transmembrane helix. This interaction appears to assist MCT expression at the cell surface. Despite the importance of short-chain fatty acids in being the main energy source in ruminant animals, the mechanism of SCFAs transport and absorption is still not fully studied. The aim of this review is to critically discuss short-chain fatty acids production and the functional role of monocarboxylate transporters in relation to the transport and absorption of these nutrients along the gastrointestinal tract of ruminants. Two major functions of monocarboxylate transporter proteins, namely the facilitation of the absorption of SCFAs in the gastrointestinal tract and the regulation of cell pH in skeletal muscles, are clearly very important for physiological homeostasis, animal welfare and productivity.**

**Key words:** Ruminants, monocarboxylates, monocarboxylate transporters, CD147.

## INTRODUCTION

Most mammals are herbivorous and are involved in the consumption of plant material high in structural carbohydrates. Consequently, these groups of animals have evolved a close symbiotic relationship with the microorganisms that reside in their gut which are engaged in the digestion of highly fibrous plant material for the host. The ruminant animal has evolved a specially adapted digestive system to enable, for the best part, a relatively efficient breakdown of feedstuffs and is divided into four different compartments, the reticulum, rumen, omasum and abomasum. The rumen is the main site of microbial digestion and is best described as a large fermentation vat which contains a complex variety of different microorganisms which act synergistically to break down feed for the host animal. After extensive fermentation by the resident microbes, the products of fermentation, mainly organic volatile fatty acids (VFAs) and microbial protein then become available to the host. Gruzdev et al. (2001) established a high proportions of rumen volatile fatty acids (acetic, butyric and propionic) in young Friesian bulls 2 hours post-feeding with mixed rations of low-degraded neutral detergent fiber in dry matter content; and these volatile fatty acids peaked for 4hrs in the rumen after feeding. Conditions in the rumen are strictly anaerobic, although small trace amounts of oxygen may be found, particularly in close proximity to the rumen wall and in ruminal gas. In the gastrointestinal tract, monocarboxylate transporters are important in the transport of short-chain fatty acids and lactate (Ritzhaupt et al., 1998a,b; Muller et al., 2002; Koho et al., 2005).

*Corresponding author. Email: aluwong_tagang@yahoo.co.uk.

**Abbreviations: SCFAs,** Short-chain fatty acids; **MCTs,** monocarboxylate transporters; **VFAs,** volatile fatty acids; **RT-PCR,** reverse transcription-polymerase chain reaction.

The aim of this review is to critically discuss volatile fatty acids or short-chain fatty acids (SCFAs) production and the functional role of monocarboxylate transporters in relation to the transport and absorption of short-chain fatty acids along the gastrointestinal tract of ruminants.

## SHORT CHAIN FATTY ACIDS PRODUCTION AND THEIR FUNCTIONS IN DIFFERENT SEGMENTS OF THE GASTROINTESTINAL TRACT OF RUMINANTS

Short chain fatty acids such as acetic, propionic, butyric, isobutyric, valeric, isovaleric, 2-methylbutyric, hexanoic and heptanoic acid, are produced in several parts of the gastrointestinal tract by microbial fermentation of dietary fibre. They constitute weak acids, but because the pH of the gastrointestinal tract, with the exception of the stomach, is nearly neutral, 90–99% of SCFAs are present as anions rather than as free acids. In all mammals examined, acetate is the main SCFA produced. Propionate and butyrate are also present in large concentrations, although their amounts can vary considerably with diet. The molar ratios of acetate to propionate to butyrate in mammals vary from approximately 7.5:15:10 to 40:40:20 (Bergman, 1990). An estimated, 60 – 70% of the energy of the epithelium of the colon is derived from SCFAs, particularly from butyrate (Scheppach et al., 1992). Butyrate also possessed other important functions in the intestinal epithelium, such as prevention of certain types of colitis (Scheppach, 1994), while acetate increases colonic blood flow and enhances ileal motility (Scheppach, 1994).

SCFAs or volatile fatty acids are the products of the anaerobic microbial fermentation of complex carbohydrates in the forestomach and large intestine. Acetate, propionate and butyrate, the predominant SCFAs, are readily absorbed and assimilated as a nutrient source by the ruminant (Bergman, 1990). Ruminants depend on SCFAs for up to 80% of their maintenance energy requirements (Bergman, 1990). Caecal SCFAs provide, on average, 8.6% of metabolizable energy intake in bovines (Siciliano-Jones and Murphy, 1989). Caecal and colonic fermentation accounts for 8.6 - 16.8% of total SCFAs production in ruminants (Ulyatt et al., 1975). In addition to their involvement as the major source of energy, the SCFAs also serve as building blocks for milk synthesis; acetate is a necessary component in the formation of milk fat, while propionate is used for glucose production, which is needed for synthesis of milk sugar (lactose). In ruminants, propionate is also the major substrate of hepatic gluconeogenesis (Herdt, 1988). Thus, effective absorption of SCFAs from the forestomach and large intestine is essential for these species. In addition, the three main SCFAs, acetate, propionate and butyrate stimulate sodium and fluid absorption in the colon and exert proliferative effects on colonocytes (Scheppach, 1994). Lactate is mostly absorbed in the small intestine (Argenzio and Southworth, 1974). In the gut, the abundance of the monocarboxylate transporter (MCT) protein in the colonic luminal membrane declines during transition from normal differentiation and proliferation in the colonic mucosa (Ritzhaupt et al., 1998). It has been established in the colon *in vivo* that a reduction in MCT1 expression, and hence butyrate transport, can lead to a reduction in intracellular butyrate levels (Daly et al., 2005). Decreased butyrate concentration results in dysfunction in the regulation of genes associated with colonic tissue homeostasis and disease prevention (Daly et al., 2005), thus, leading to impairment of animal welfare.

## MONOCARBOXYLATE TRANSPORTERS

Monocarboxylic acid transporters (MCTs) members of SLC16A family are proton-linked transporters that play a crucial role in cellular metabolism. To date, fourteen MCT related sequences have been identified in mammals through sequence homology; however, only seven isoforms have been functionally characterized (Halestrap and Meredith, 2004; Murakami et al., 2005). These isoforms differ in terms of tissue distribution, substrate specificities and affinities with only four isoforms (MCT1-4) characterized as proton-dependent monocarboxylate transporters (Halestrap and Meredith, 2004; Bonen et al., 2006).

In all species studied, efflux of lactate and protons is facilitated mainly by MCTs, which transport a proton and a lactate anion through the cell membrane (Juel, 1998; Halestrap and Price, 1999). Among monocarboxylates, the transport of lactate is quantitatively the most important, but MCTs also transport other monocarboxylates such as butyrate, acetate and propionate, which are important especially in the gastrointestinal tract (Halestrap and Price, 1999). Of the 14 different MCT isoforms (MCT1-MCT14) identified so far, MCT1, MCT2 and MCT4 are the best characterized and known to transport lactate (Halestrap and Meredith, 2004). These three isoforms have different species- and tissue-specific distributions (Halestrap and Price, 1999). TAT1 (MCT10) has been shown to transport aromatic amino acids (Halestrap and Meredith, 2004), and MCT8 to be an active and specific thyroid hormone transporter (Friesema et al., 2003). In addition, MCTs in the epithelium of the small intestine, colon and blood-brain barrier provide routes for many carboxylated pharmaceutical agents (Enerson and Drewes, 2003). All MCTs are membrane proteins, with 12 transmembrane regions and cytoplasmic N- and C- terminal ends (Poole et al., 1996; Halestrap and Price, 1999). They transport a monocarboxylate anion and a proton together through the cell membrane according to the electrochemical gradients of substrates. MCT-1 and 4 need a chaperone protein, CD147 (also known as basigin, EMMPRIN, HT7 or OX-47), in muscle (Halestrap and Price 1999; Juel and Halestrap 1999), red blood cells (RBCs) (Koho et al., 2002) and the intestine

(Buyse et al., 2002). The suggested model of the topology of CD147 and MCT1 in the plasma membrane is a dimmer of CD147 associated with two MCT1 molecules such that the C-terminus of CD147 in the cytosol is close to the C-terminus of its partner CD147 and to the C- and N- termini of an associated MCT1 molecule (Wilson et al., 2002).

## FUNCTIONAL ROLE OF MONOCARBOXYLATE TRANSPORTERS IN DIFFERENT PARTS OF THE GASTROINTESTINAL TRACT OF RUMINANTS

In the gastrointestinal tract, monocarboxylate transporters are important in the transport of short-chain fatty acids and lactate (Ritzhaupt et al., 1998a, b; Muller et al., 2002, Koho et al., 2005). The two major functions of monocarboxylate transporter proteins, namely the facilitation of the absorption of SCFAs in the gastro-intestinal tract and the regulation of cell pH in skeletal muscles, can thus be assumed to be very important for physiological homeostasis and also for animal welfare.

The transport of short-chain monocarboxylates across the plasma membrane in most cells is largely dependent on a family of specific MCTs. Kirat et al. (2005, 2006) established that MCT1 is expressed along the gastrointestinal tract of preruminant calves, and adult sheep, respectively. Thus, it can be suggested that MCT1 may possibly play a vital role in the transport of SCFAs across the ruminant gastrointestinal tract. Kirat et al. (2006) using reverse transcription-polymerase chain reaction (RT-PCR) established that MCT1 mRNA was highly expressed in bovine large intestinal mucosa. Both immunohistochemistry and confocal laser microscopy verified that the MCT1 protein was abundant in the surface epithelium of the large intestine, and the amount decreased from the opening of the crypt to its base. In the immunopositive cells, MCT1 was primarily localized in the basolateral membranes of epithelium lining the large intestine. MCT1 is an obligatory symporter that carries a dissociated proton-monocarboxylate pair with each transport cycle (Halestrap and Meredith, 2004). Also, Kirat et al. (2006) using RT-PCR revealed the presence of mRNA encoding for MCT1 in all regions of the caprine gastrointestinal tract. Quantitative western blot analysis also showed that the level of MCT1 protein was in the order of rumen ≥ reticulum > omasum > caecum > proximal colon > distal colon > abomasum > small intestine. Amongst the stratified squamous epithelial cells of the forestomach, MCT1 was predominantly expressed on the cell boundaries of the stratum basale and stratum spinosum. Double-immunofluorescence confocal laser-scanning microscopy confirmed the co-localization of MCT1 with its ancillary protein, CD147 in the caprine gastrointestinal tract (Kirat et al., 2006). Kirat et al. (2007) established the precise cellular localization of MCT4, along with its co-existence with its chaperone, CD147 in the ruminant gastrointestinal tract. Using quantitative western blot analysis, they demonstrated that the abundance of MCT4 protein was in the order of forestomach > large intestine > abomasum ≥ small intestine. Immunohistochemistry and immunofluo-rescence confocal laser microscopy also showed that MCT4 in the forestomach was confined to the cell membranes of strata corneum and granulosum, while diffuse cytoplasmic staining for MCT4 was visualized in strata spinosum and basale. In the epithelium cells lining the abomasum, MCT4 immunoreactive positivities were predominantly localized on the basolateral membranes. In the small intestine, MCT4 was localized at the brush borders and the basolateral membranes of the epithelial cells lining the villi, however, it was mostly found on the apical membranes of the crypt cells.

In the large intestine, the immunoreactivity for MCT4 differed between the surface epithelium and the crypts; in the surface epithelium, MCT4 was mainly localized at the apical membranes, whereas in the crypts it was predominantly expressed on the basolateral membranes of the lining epithelial cells. MCT4 was remarkably co-existed with CD147 along the bovine gastrointestinal tract.

## CONCLUSION

Short-chain fatty acids (acetate, propionate and butyrate) are the end products of anaerobic microbial fermentation of carbohydrates in ruminant gastrointestinal tract. They represent the most predominant anions in the ruminant forestomach and large intestine. They are readily absorbed into the blood stream and transported to body tissues where they are used for hepatic gluconeogenesis, lipogenesis in peripheral tissues and milk synthesis. The transport of short-chain monocarboxylates across the plasma membrane in most cells is largely dependent on monocarboxylate transporter family. There is a potential functional collaboration between MCT1 and MCT4; this may provide new insights into the mechanisms that mediate the transport of short-chain fatty acids and other monocarboxylates in the different segments of the ruminant gastrointestinal tract.

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