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Metabolism in ruminants and its association with blood biochemical analytes

Metabolismo en rumiantes y su asociación con analitos bioquímicos sanguíneos

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ABSTRACT

The present study is an analysis of scientific elements on the metabolism of ruminants: polysaccharides, proteins and lipids. Where i) the fermentative digestion carried out by microorganisms, ii) the posruminal digestion and absorption and iii) the metabolism of each monomer is associated with the blood analytes that give us an approximation to the nutritional metabolism of the animal, also confer information on alterations and adjustments homeostatic. This review emphasizes the metabolism of monosaccharides, amino acids, and fatty acids. Therefore, the revised information aims to make the understanding of catabolic and anabolic processes in ruminant nutrition.

Keywords: glucose, lipids, polysaccharides, proteins and urea.

RESUMEN

El presente estudio es un análisis de elementos científicos sobre el metabolismo de los rumiantes: polisacáridos, proteínas y lípidos. Donde i) la digestión fermentativa realizada por microorganismos, ii) la digestión y absorción posruminal y iii) el metabolismo de cada monómero, se asocian con analitos sanguíneos que otorgan una aproximación al metabolismo nutricional del animal, además confieren información sobre alteraciones y ajustes homeostáticos. Esta revisión hace énfasis en el metabolismo de monosacáridos, aminoácidos y ácidos grasos. Por lo tanto, la información revisada pretende hacer más accesibles los procesos catabólicos y anabólicos en la nutrición de los rumiantes.

Palabras claves: glucosa, lípidos, polisacáridos, proteínas y urea.

INTRODUCTION

Mammals classified as ruminants are characterized by the morphophysiological adaptation of their digestive system ([Resende Jr et al., 2019](#); [Rotta et al., 2014](#)), divided into four chambers: I) reticulum, II) rumen, III) omasum and IV) abomasum ([Qiyu et al., 2019](#)). Abomasum secretes digestive hydrolases and its function is similar to that of monogastric stomachs ([Agarwal et al., 2015](#)). Ruminants specialize in their ability to feed on pasture and forage ([Puppel y Kuczyńska, 2016](#)), as they can degrade structural

polysaccharides for example: cellulose, hemicellulose and pectin (DePeters y George, 2014), very poorly digestible for non-ruminant species (Kittelmann *et al.*, 2013; Zeng *et al.*, 2017). Food degradation is mainly carried out by fermentative digestion, carried out by microorganisms present in the rumen (Ginane *et al.*, 2015; Wallace *et al.*, 2017). The molecules resulting from ruminal fermentation are used to satisfy the animal's physiological processes (Kittelmann *et al.*, 2013; Li *et al.*, 2019^a). The quantification of biochemical analytes in plasma and/or serum, provide an approximation to nutritional metabolism (García *et al.*, 2015). They also confer information on homeostatic alterations and adjustments (Moyano *et al.*, 2018). For this reason, it is important to understand the catabolism and anabolism processes that are carried out in the ruminant to understand the levels of analytes present (Puppel y Kuczyńska, 2016). Because of this, it is necessary to increase our understanding of the metabolism of monosaccharides, amino acids (aa) and fatty acids. Therefore, a bibliographic review was carried out on its metabolism in ruminants and its association with different biochemical analytes.

Abbreviations

aa	amino acids	His	histidine
AcAc	acetoacetate	Ile	isoleucine
AGNE	unesterified fatty acids	K ⁺	potassium ion
AGV	volatile fatty acids	Leu	leucine
ALB	albumin	Lys	lysine
Arg	arginine	Met	metionina
C=O	carbonyl group	Na ⁺	sodium ion
C16:0	palmitic	NH ₃	ammonia
C ₃ H ₃ O ₃	pyruvate	NNP	non-protein nitrogen
C ₆ H ₁₂ O ₆	glucose	pH	hydrogen potential
CO ₂	carbon dioxide	Phe	phenylalanine
COL	cholesterol	PLP	pyridoxal phosphate cofactor
COOH	carboxyl group	TAG	triacylglycerols
CH ₄	methane	Thr	threonine
FAD	flavin-adenine dinucleotide	Trp	tryptophan
Glu	glutamic	Val	valine
H ₂ CO ₃	carbonic	VLDL	very low density lipoproteins
HCl	Hydrochloric	β-HBA	β- hydroxybutyrate
HCO ₃ ⁻	hydrogencarbonate anion		

The Rumen

The rumen is an anaerobic fermentation chamber (Armato *et al.*, 2016), with an acid to neutral hydrogen potential (pH) of 5.5 to 7.0 (Jiang *et al.*, 2017); this being the main determinant of the type and number of microorganisms (Resende Jr *et al.*, 2019) and a temperature ranging from 38 to 42 °C (Pourazad *et al.*, 2016; Yazdi *et al.*, 2016). The ruminal ecosystem is made up of three groups: I) bacteria, its concentration is 1 x 10¹⁰

and 1×10^{11} /mL of ruminal fluid (Valente *et al.*, 2016), and it is related to the energy content of the diet (Krause *et al.*, 2013); Furthermore, non-protein nitrogen (NNP), like urea, must be converted to ammonia (NH_3) for it to be used by bacteria (DePeters y George, 2014; Wallace *et al.*, 2017), transforming poor-quality protein into high quality protein (Puppel y Kuczyńska, 2016; Jin *et al.*, 2018); group II) ciliated protozoa, its concentration ranges from 1×10^4 to 1×10^6 /mL of rumen fluid, its function is to control the number of bacteria in the rumen (Francisco *et al.*, 2019), they wrap starch that passes into the intestine, being a source of glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) for the ruminant (Wallace *et al.*, 2017), they do not synthesize protein from NNP (Jin *et al.*, 2018) most are of the *Isotricha* or *Entodinium* genus (Gebreegziabher, 2016), and group III) fungi, they are found in a concentration of 1×10^3 to 1×10^5 /mL of ruminal fluid, they have cellulolytic activity mainly in mature forages (Valente *et al.*, 2016); some species are *Neocallimastix frontalis*, *Caecomyces communis* and *Piromyces communis* (Krause *et al.*, 2013).

The Amilolytic-Cellulolytic Ruminal Microbiota and Anaerobic Fermentation

The degradation of polysaccharides present in forages is carried out by cellulolytic bacteria (*Bacteriodes succinogenes*, *Ruminococcus albus*), amilolytics (*Bacteroides amylophilus*, *Streptococcus bovis*), hemicellulolytics (*Butyrivibrio fibrisolvens*, *Bacteroides ruminocolanos*) and pectinolytics (*Lachnospira multiparus*, *Succinivibrio dextrinosolvens* (Valente *et al.*, 2016), which obtain $\text{C}_6\text{H}_{12}\text{O}_6$ and other monosaccharides such as xylose and fructose-6-phosphate, from cellulose and hemicellulose (Krause *et al.*, 2013). The monomers are absorbed by microorganisms and they form a nicotinamide adenine dinucleotide in its reduced form ($\text{NADH}+\text{H}^+$), pyruvate ($\text{C}_3\text{H}_3\text{O}_3$) and adenosine triphosphate (ATP) for its growth and maintenance (Wallace *et al.*, 2017; Francisco *et al.*, 2019). Fermentative digestion is anaerobic (Kittelmann *et al.*, 2013; Yazdi *et al.*, 2016), so $\text{C}_3\text{H}_3\text{O}_3$ works as an electron collector, to generate NAD^+ and ATP, removing $\text{NADH}+\text{H}^+$ (Górka *et al.*, 2017).

Volatile fatty acids (AGV): acetic ($\text{CH}_3\text{-COOH}$), propionic ($\text{CH}_3\text{-CH}_2\text{-COOH}$) and butyric ($\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$) are the main end products of fermentative digestion (Aydin *et al.*, 2017; Li *et al.*, 2019^a); they are absorbed through the rumen wall and incorporated into the circulation through the portal vein (Resende Jr *et al.*, 2019). They represent between 70-80% of the ruminant's energy fuel (Mikołajczyk *et al.*, 2019).

The ruminal flora synthesizes $\text{CH}_3\text{-COOH}$ from the decarboxylation of $\text{C}_3\text{H}_3\text{O}_3$ in acetyl coenzyme A, releasing a carbon (Gebreegziabher, 2016; Chishti *et al.*, 2020). For the formation of $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$ two acetyl coenzyme A are required (Górka *et al.*, 2017; Resende Jr *et al.*, 2019). There are two routes for the formation of $\text{CH}_3\text{-CH}_2\text{-COOH}$: I) direct reductive route, $\text{C}_3\text{H}_3\text{O}_3$ passes to lactate, and this to acrylyl-coenzyme A (Aydin *et al.*, 2017), and II) random route, a carbon to $\text{C}_3\text{H}_3\text{O}_3$ and the oxaloacetate formed is transformed into succinate; $\text{CH}_3\text{-CH}_2\text{-COOH}$ is subsequently synthesized, losing one carbon and forming molecular dioxygen (Krehbiel, 2014; Gebreegziabher, 2016). In

addition, carbon dioxide (CO_2) and methane (CH_4) are formed and are eliminated by belching (Teklebrhan *et al.*, 2020; Toral *et al.*, 2017). CH_4 synthesis is necessary for the production of oxidized cofactors in the routes for the formation of $\text{CH}_3\text{-COOH}$ and $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$ (Kozłowska *et al.*, 2019). The bacteria responsible for this function are *Methanobrevibacter ruminantium*, *Methanobacterium formicicum* and *Methanomicrobium mobile* (Baruah *et al.*, 2019).

Figure 1 shows AGV synthesis. The rumen concentration of $\text{CH}_3\text{-COOH}$, $\text{CH}_3\text{-CH}_2\text{-COOH}$ and $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$ in animals fed on forage. It ranges 70: 20: 10% respectively, and in animals fed mainly with cereals it fluctuates 60: 30: 10% (Gebreegziabher, 2016).

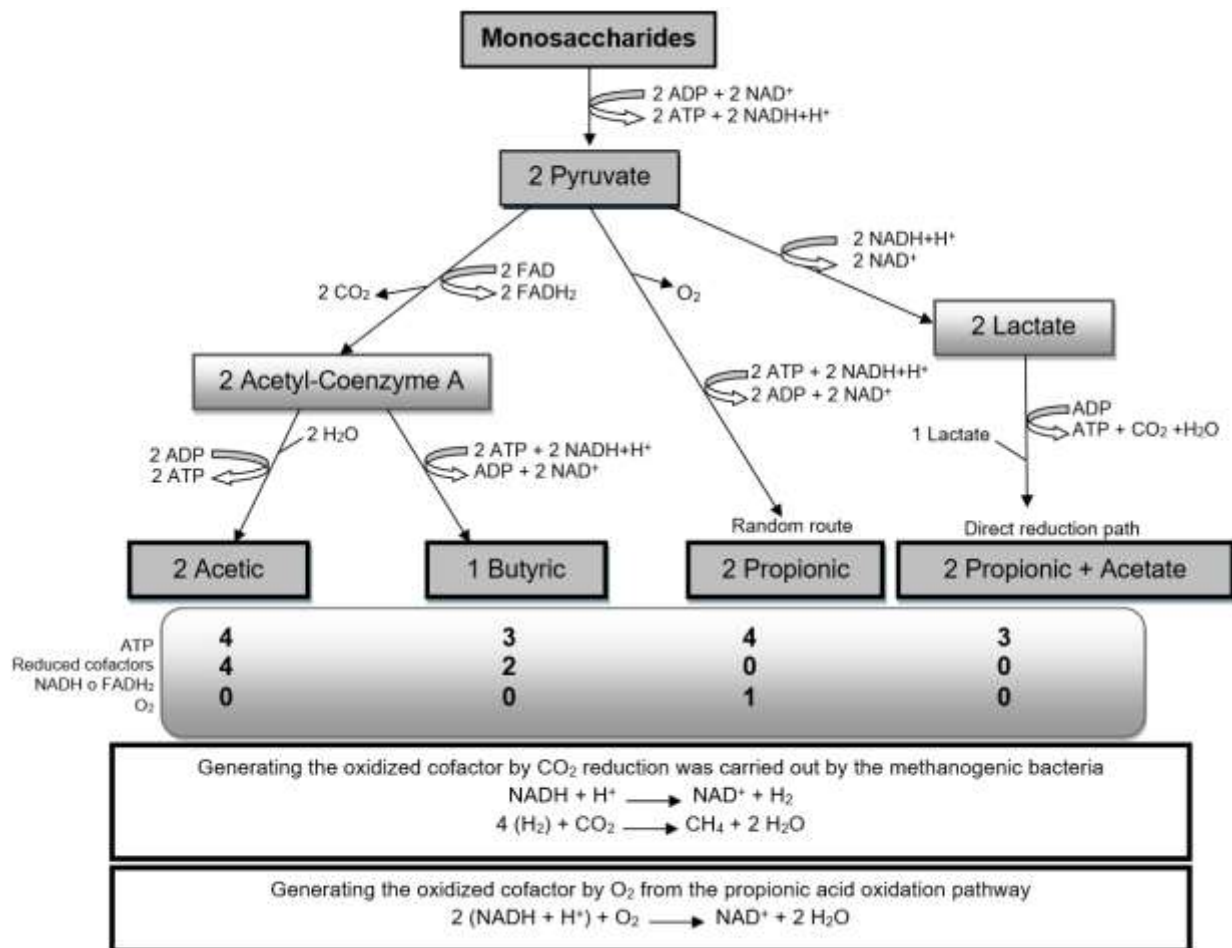


Figure 1. Synthesis of volatile fatty acids from monosaccharides in the rumen

Source: synthesized information of (Gebreegziabher, 2016)

The Proteolytic Ruminal Microbiota and Anaerobic Fermentation

The protein components supplied in the diet are fermented by proteolytic bacteria *Bacteroides amylophilus*, *Bacteroides ruminicola*, and some strains of *Butyrivibrio*

fibrisolvens (García *et al.*, 2014), through their microbial proteases, releasing peptides (Alves *et al.*, 2014; Rostom y Shine, 2018). These are absorbed by the microorganism, where the peptidases hydrolyze the peptide bonds, releasing aa, used to translate own proteins or catabolize them to release energy (Li *et al.*, 2019^b; Silva *et al.*, 2016). The final product is NH₃ (Khezri *et al.*, 2016; Carvalho *et al.*, 2019), which serves as a nitrogen substrate for bacteria (Valente *et al.*, 2016). NH₃ is absorbed by passive diffusion through potassium ion channels (K⁺), located in the rumen membrane (García *et al.*, 2014), by portal circulation it reaches the liver where it is synthesized in urea (Rostom y Shine, 2018).

Urea synthesis begins in the mitochondrial matrix (Shi *et al.*, 2019) with the binding of the hydrogen carbonate anion (HCO₃⁻) and NH₃, by means of carbamoyl phosphate synthetase. Carbamoyl phosphate binds to ornithine, via ornithine transcarbamoylase, generating citrulline. This is transported to the cytoplasm where it reacts with aspartate by means of argininosuccinate synthase, forming argininosuccinate. Subsequently, argininosuccinate lyase divides it, forming arginine (Arg) and fumarate (Hristov *et al.*, 2019). Lastly, Arg catalyzes hydrolysis to synthesize ornithine, water (H₂O) and urea (Gebreegziabher, 2016) (figure 2).

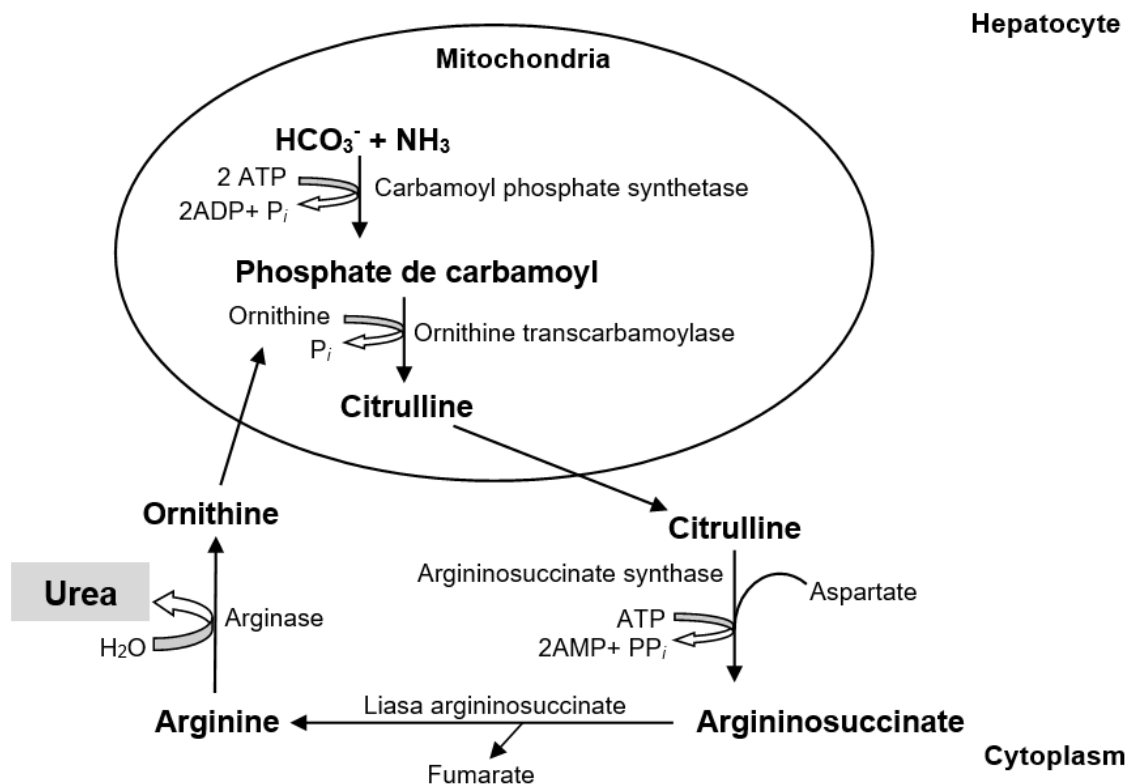


Figure 2. Urea Synthesis
Source: synthesized information of (Shi *et al.*, 2019).

The urea goes back to the blood circulation where it has three metabolic routes: 1.) returns to the rumen via saliva or through the epithelial layers of rumen with the help of transport protein UT-B to be converted in NH_3 (García *et al.*, 2014; Carvalho *et al.*, 2019), 2) excreted in the urine or feces (Schuba *et al.*, 2017; Li *et al.*, 2019^b) or, 3) to be part of NNP of milk (Alves *et al.*, 2014; Jin *et al.*, 2018) (figure 3).

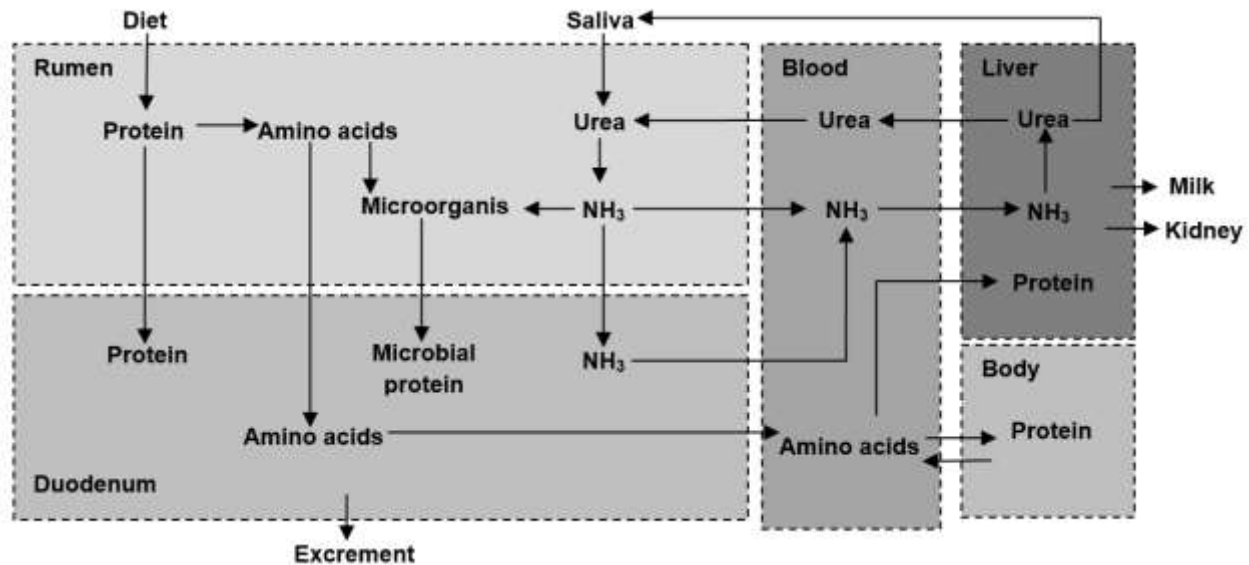


Figure 3. General metabolism of proteins in the rumian

Source: synthesized information of (Li *et al.*, 2019^b)

The Lipolytic Ruminal Microbiota and Anaerobic Fermentation

The microorganisms in charge of catabolizing the lipid components of the diet are: *Anaerovibrio lipolytica*, *Butyrivibrio fibrisolvens*, *Treponema bryantii*, *Eubacterium* spp., *Fusocillus* spp. and *Micrococcus* spp. (Valente *et al.*, 2016). Bacterial lipases by hydrolysis release unesterified fatty acids (AGNE) and glycerol (Prieto *et al.*, 2016); In addition, amino alcohols (derived from phospholipids) and galactose (from galactolipids) (Toral *et al.*, 2018). Glycerol, amino alcohols and galactose are metabolized to AGV (Silva *et al.*, 2014; van Cleef *et al.*, 2018). The AGNE that are free in the rumen, carry out a microbial hydrogenation process (Tran *et al.*, 2017; Toral *et al.*, 2017), result of the addition of hydrogen to saturated fatty acids, to form unsaturated fatty acids with double bonds (Francisco *et al.*, 2019). This mechanism is another way to eliminate the hydrogens that result from the catabolism of the polysaccharides (Osorio *et al.*, 2015; Prieto *et al.*, 2016).

The absorption of AGV is carried out in the rumen wall (80%), in omasum (10%), and the rest passes to the abomasum to be absorbed in the duodenum (Yazdi *et al.*, 2016). AGVs passively diffuse into the ruminal epithelium (Agarwal *et al.*, 2015; Yohe *et al.*, 2019). The hydrogen necessary for the AGVs to dissociate in the epithelium is donated by carbon

dioxide (H_2CO_3), forming CO_2 and H_2O , from the dissociation a hydrogen is obtained to bind to the AGVs and a HCO_3^- molecule is formed in the lumen of the rumen. Therefore, this process helps buffer the rumen pH (Wang *et al.*, 2016).

The absorption of AGV is carried out in the same way for all, although inside the epithelial cells of the rumen its conformation changes (Qumar *et al.*, 2016). A part of the $\text{CH}_3\text{-COOH}$ is completely oxidized inside the cells, as an energy source; while the rest is absorbed without being altered, passing to the liver through the portal vein (Loncke *et al.*, 2015). 80% of the $\text{CH}_3\text{-COOH}$ that reaches the liver escapes oxidation, passing into the general circulation to be used by other tissues (Qumar *et al.*, 2016).

In the cytoplasm, the conversion of $\text{CH}_3\text{-COOH}$ to acetyl-Coenzyme A is catalyzed by acetyl-Coenzyme A synthetase (Chishti *et al.*, 2020). Most of it is oxidized in the Krebs cycle or is used for fatty acid synthesis in hepatocytes (Yohe *et al.*, 2019). A fraction of $\text{CH}_3\text{-CH}_2\text{-COOH}$ is degraded and converted to lactate (2-5%) before or during absorption; the rest passes in the portal circulation to the liver, where the hepatocytes synthesize it in $\text{C}_6\text{H}_{12}\text{O}_6$, via glycogenesis (Loncke *et al.*, 2015). To enter the Krebs cycle, propionyl-Coenzyme A through propionyl-Coenzyme A carboxylase, forms methylmalonyl-Coenzyme A, and then succinyl-Coenzyme A is formed (Gebreegziabher, 2016). $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$ is converted almost entirely to β -hydroxybutyrate (β -HBA) in the rumen mucosa (Agarwal *et al.*, 2015). This ketone body represents 80% of the ketones formed (Górka *et al.*, 2017). $\text{CH}_3\text{-COOH}$ and β -HBA are used for the synthesis of fatty acids in adipose tissue and the mammary gland (García *et al.*, 2015; Song *et al.*, 2018).

Postruminal Digestion and Absorption

Although the ruminant is characterized by microbial fermentation in the rumen (Hristov *et al.*, 2019), post-ruminal digestion is vital, since it has lipids, proteins and some non-structural polysaccharides that escape from fermentation (Agarwal *et al.*, 2015). The unfermented food along with microbial protein, passes to the omasum through the reticulo-omasal hole, where AGV, NH_3 , H_2O , sodium ion (Na^+) and K^+ are absorbed (Hussain *et al.*, 2013; Freitas Jr *et al.*, 2019). Subsequently, they pass to the abomasum containing hydrochloric acid (HCl) and pepsin (Rotta *et al.*, 2014). Food is mixed, passing into the duodenum (Hristov *et al.*, 2019). The starch and disaccharides that escape from the ruminal digestion are hydrolyzed by pancreatic amylases, obtaining monosaccharides (Rotta *et al.*, 2014).

Absorption takes place in the villi of the enterocytes (Harmon, 2009). Monosaccharides are transported against their concentration gradient by means of the Na^+ co-transporter (Harmon y Swanson, 2020). The ATPase- Na^+ - K^+ pump creates the energy-contributing Na^+ concentration gradient (Bergman *et al.*, 2019).

Another form of transport for $\text{C}_6\text{H}_{12}\text{O}_6$ is the GLUT2 transporter (Harmon, 2009). The protein that reaches the small intestine comes from the diet that escapes from

fermentation, endogenous protein (García *et al.*, 2015) and that contained in the microorganisms that are linked to food (Batista *et al.*, 2016; Golshan *et al.*, 2019). Catabolism begins in the abomasum due to pepsin and acid hydrolysis; later in the duodenum by pancreatic and duodenal enzymes (trypsinase, chymotrypsinase and carboxypeptidase), which break peptide bonds to release aa and small peptides for their absorption in jejunum and ileum (Emery, 2015; Hristov *et al.*, 2019). Absorption consists of transport through Na^+ dependent, energy consumption is associated with the continuous flow of Na^+ to the outside, as a result of the activity of the ATPase- Na^+ - K^+ pump (Silva *et al.*, 2016). The Na^+ that enters the cell in favor of a concentration gradient, is bound to an aa molecule through the cell membrane (Emery, 2012; Rostom y Shine, 2018).

The lipids that reach the abomasum in the form of AGNE represent between 70 and 80%, the rest are phospholipids of microbial origin (Aibibula *et al.*, 2015; Toral *et al.*, 2018). The latter are emulsified by bile salts and hydrolyzed by pancreatic lipases to release AGNE (Dawson y Karpen, 2015; Kohan *et al.*, 2015). The micelle is formed from bile salts, saturated AGNE, triacylglycerols (**TAG**) and lecithin (Cao *et al.*, 2018), transporting itself to the villi of the enterocytes (Park *et al.*, 2019). AGNE of less than 12 carbons are absorbed and transported by portal vein to the liver linked by non-covalent bonds in albumin (**ALB**) (Dawson y Karpen, 2015). In contrast, AGNE of 12 or more carbons are esterified to form TAGs and phospholipids (Vargas, 2019). TAGs, small amounts of mono and diacylglycerols, phospholipids and cholesterol (**COL**) are bound to apoproteins to form chylomicrons and *very low density lipoproteins* (**VLDL**), which leave the lymphatic system, to be incorporated into the bloodstream (Kohan *et al.*, 2015; Prieto *et al.*, 2016). Lipids are absorbed by diffusion or pinocytosis (Walther y Farese Jr, 2012).

Monosaccharide Metabolism in Ruminants

The blood stream is the means by which the absorbed nutrients are directed to the liver and other organs for catabolism or anabolism, depending on cellular need (Goyal y Longo, 2015). Enzymes play a very important role in metabolism, as they are catalytic proteins for specific reactions (Jindal y Warshel 2017); Without them, biological reactions would be very slow for cell life (Ramsay *et al.*, 2019). Its function is to temporarily bind to a molecule, to apply atomic changes (Menger y Nome, 2019). Monosaccharide metabolism revolves around the supply and destination of $\text{C}_6\text{H}_{12}\text{O}_6$, with this monomer being the main source of energy for cells (Hooijberg *et al.*, 2017). The catabolic route of $\text{C}_6\text{H}_{12}\text{O}_6$ is glycolysis, carried out in the cellular cytoplasm (Dashty, 2013) This process consists of eight reactions: 1) glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) enters the cytoplasm to be phosphorylated (addition of a phosphate group), starting from ATP. This reaction is catalyzed by hexokinase. The resulting glucose-6-phosphate ($\text{C}_6\text{H}_{11}\text{O}_9\text{P}$) (aldohexose) abounds in all cells, since the vast majority of $\text{C}_6\text{H}_{12}\text{O}_6$ that enters the cytoplasm ends up being phosphorylated, in order to prevent that it can cross the cytoplasmic membrane back and diffuse into the

extracellular medium ([Donnelly y Finlay, 2015](#)); 2) $C_6H_{11}O_9P$ has isomerization [one molecule is transformed into another that has the same atoms, but arranged differently - the carbonyl group ($C=O$) - is replaced] and is transformed into fructose-6-phosphate (ketohexose) . Glucose-6-phosphate isomerase catalyzed reaction ([Dashty, 2013](#)); 3) fructose-6-phosphate, is phosphorylated from ATP, at carbons 1 and 6 to give fructose-1,6-bisphosphate. Phosphofructokinase catalyzed reaction ([Ashrafi y Ryan, 2017](#)); 4) Fructose-1,6-bisphosphate is divided into two: glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. Aldose catalyzed reaction ([Watts y Ristow, 2017](#)); 5) triose phosphate isomerase catalyzes the conversion of dihydroxyacetone phosphate to obtain more glyceraldehyde-3-phosphate ([Bommer et al., 2020](#)); 6) glyceraldehyde-3-phosphate is oxidized and phosphorylated, at carbons 1 and 6 forming 1,3-bisphosphoglycerate by glyceraldehyde-phosphate dehydrogenase ([Poher et al., 2018](#)). Subsequently, it transfers its phosphate group, to synthesize ATP and it is transformed into 3-phosphoglycerate. Phosphoglycerate kinase catalyzed reaction ([Dashty, 2013](#)); 7) 3-phosphoglycerate exhibits isomerization of C3 to C2 and it is transformed into 2-phosphoglycerate by phosphoglycerate mutase ([Donnelly y Finlay, 2015](#)). Subsequently, enolase promotes the formation of a double bond, eliminating an H_2O molecule and forming phosphoenolpyruvate ([Bommer et al., 2020](#)) and 8) phosphoenolpyruvate transfers its phosphate group, to synthesize ATP and it is transformed into $C_3H_3O_3$, a reaction catalyzed by pyruvate kinase (figure 4).

$C_3H_3O_3$ leaves the cytoplasm and enters the mitochondrial matrix, using the proton-motor force generated by the respiratory chain ([Poher et al., 2018](#)). For each $C_6H_{12}O_6$, two $C_3H_3O_3$, two ATP, two $NADH+H^+$, two hydrogenions and two H_2O molecules are generated ([Dashty, 2013](#); [Watts y Ristow, 2017](#)). Aerobic cells metabolize $C_3H_3O_3$ to acetyl-Coenzyme A, by means of pyruvate dehydrogenase ([Edinburgh et al., 2017](#)), allowing its entry into the Krebs cycle for its participation in oxidative phosphorylation ([Bergman et al., 2019](#)).

For each acetyl-Coenzyme A that enters the Krebs cycle, 12 ATP are produced. This process is an essential source of intermediaries for other metabolic pathways, eg. eg, glycogenogenesis in the liver and striated muscle ([Dashty, 2013](#); [Edinburgh et al., 2017](#)), the pentose phosphate pathway (Figure 4) and lipid synthesis and aa. The pentose phosphate pathway, is an alternate metabolic pathway that does not produce ATP ([Kohan et al., 2015](#)), synthesizes reducing equivalents such as nicotinamide adenine dinucleotide (**NADPH**), for the de novo synthesis of fatty acids, steroids, maintenance of glutathione for antioxidant activity ([Chen et al., 2016](#)) and ribose sources for the synthesis of nucleic acids and nucleotides ([Norris et al., 2016](#)).

The triose phosphate intermediate of glycolysis forms the glycerol moiety in TAGs ([Edinburgh et al., 2017](#)). On the other hand, $C_3H_3O_3$ and Krebs cycle intermediaries supply the carbon skeletons for the synthesis of aa ([Valdebenito et al., 2016](#)) and acetyl-

Coenzyme A is the precursor of AGNE, COL and steroid hormones (Edinburgh *et al.*, 2017). Gluconeogenesis synthesizes $C_6H_{12}O_6$ from lactate, aa and glycerol (Cantalapiedra *et al.*, 2015; Campos *et al.*, 2018), in the cytoplasm and mitochondria of hepatocytes (Chen *et al.*, 2016; Qaid y Abdelrahman, 2016). In this route, six ATP are consumed for each $C_6H_{12}O_6$ produced (Gebreegziabher, 2016) and the CH_3-CH_2-COOH propionate is the only glycogenic AGV (Wallace *et al.*, 2017).

The importance of glycogenesis in ruminants (figure 4), is due to the fact that small amounts of $C_6H_{12}O_6$ are absorbed by the body from the digestive tract and its ability to store glycogen in the liver is limited (Qaid y Abdelrahman, 2016).

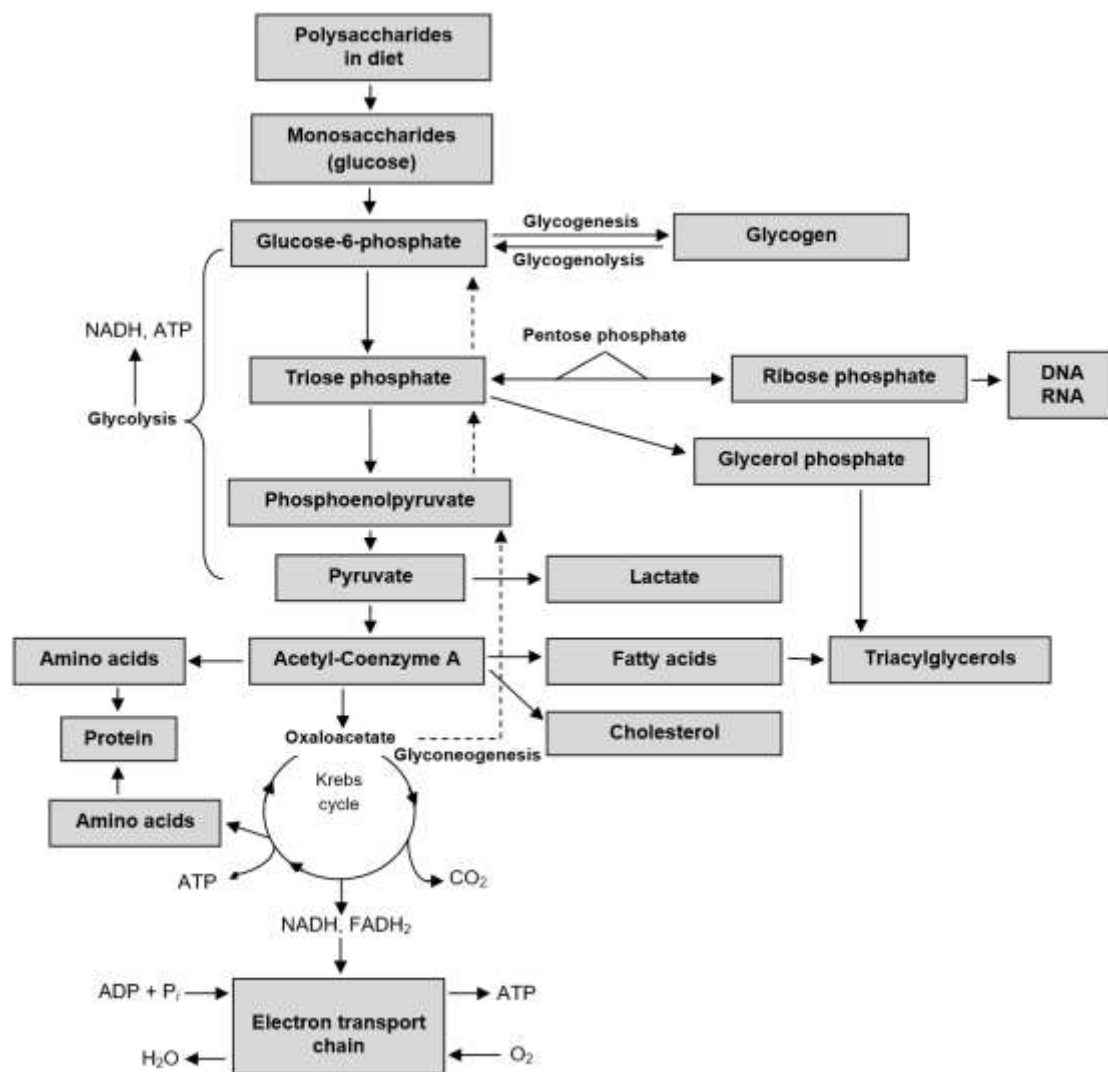


Figure 4. General metabolism of monosaccharides

Source: synthesized information of (Dashty, 2013)

Fatty Acid Metabolism in Ruminants

Lipid metabolism mainly depends on fatty acids and COL (Watts y Ristow, 2017). The source of long-chain AGNE is provided by diet or by de novo synthesis from acetyl-Coenzyme A, which is derived from monosaccharides or aa carbon skeletons (Walther y Farese Jr, 2012). The synthesis of fatty acids begins in the mitochondria with the formation of acetyl-Coenzyme A, from the oxidation of $\text{CH}_3\text{-COOH}$ and $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$ (Vargas, 2019). Within the mitochondria, acetyl-Coenzyme A is produced; however, the mitochondrial membrane is impervious to its passage. Therefore, the tricarboxylate system and the action of citrate synthetase are required to convert acetyl-Coenzyme A to citrate and allow its passage into the cell cytoplasm (Civeira *et al.*, 2013; Nunes-Nesi *et al.*, 2013).

Once in the cytoplasm, the citrate is transformed again into acetyl-Coenzyme A by means of ATP-citrate lyase, also obtaining oxaloacetate and adenosine diphosphate (ADP) (Walther y Farese Jr, 2012). As the process for the synthesis of fatty acids is endergonic (it accumulates energy from carbons), acetyl-Coenzyme A presents carboxylation [a carboxyl group (COOH) is structured in the molecule], through its union with HCO_3^- in a reaction catalyzed by acetyl-Coenzyme A carboxylase (García *et al.*, 2014).

Oxaloacetate is reduced by malate dehydrogenase to malate, and this in turn is converted to $\text{C}_3\text{H}_3\text{O}_3$ by malate dehydrogenase, giving the electron donor nicotinamide adenine dinucleotide phosphate in its reduced form ($\text{NADPH}+\text{H}^+$) (Watts y Ristow, 2017; Vargas, 2019). From malonyl-Coenzyme A, the synthesis of fatty acids is carried out by elongation, using fatty acid synthase (Du *et al.*, 2018). This protein complex performs synthesis, reduction, dehydration, and reduction again, condensing the malonyl-Coenzyme A groups with acetyl-Coenzyme A (Civeira *et al.*, 2013; Norris *et al.*, 2016). In the elongation, groups of two carbons are added to the fatty acid, obtaining palmitic (C16:0) as the final fatty acid (Shi *et al.*, 2018).

Fatty acids (figure 5) can be oxidized to acetyl-Coenzyme A by mitochondrial β -oxidation, or esterified with glycerol to form TAG and function as the body's main energy reserve (Osorio *et al.*, 2015). TAG synthesis begins with the formation of glycerol-3-phosphate (Fong *et al.*, 2016), later acyl-Coenzyme A fatty synthase activates fatty acids and three of them are esterified to the molecule (Civeira *et al.*, 2013).

In TAG catabolism, the ester bonds at C1 or at C3 are hydrolyzed, obtaining AGNE. Hormone sensitive lipase catalyzed reaction (McFadden, 2020). AGNE are transported in the bloodstream, through non-covalent binding with ALB, where they are captured and oxidized by myocytes or hepatocytes, or stored by adipocytes (Edinburgh *et al.*, 2017). The β -oxidation is carried out in the mitochondrial matrix (Morita *et al.*, 2016), being carried out by means of the activation of fatty acids by means of thiosinase in acyl-Coenzyme A (Walther y Farese Jr, 2012); this process requires ATP to form adenylyl (Fukao *et al.*, 2014). Activated acyl-Coenzyme A enters the mitochondrial matrix through carnitine

palmitoyltransferase (Nunes-Nesi *et al.*, 2013; Morita *et al.*, 2016), and it is oxidized by fatty acyl-Coenzyme A dehydrogenase (Houten y Wanders, 2010). Hydrogen atoms are accepted by flavin-adenine dinucleotide (FAD) which is reduced to FADH₂ (Norris *et al.*, 2016). Subsequently, enoyl-Coenzyme A hydratase introduces H₂O into the newly formed double bond between C2 and C3 (Kong *et al.*, 2017) and β -hydroxyacyl Coenzyme A dehydrogenase forms 3-ketoacyl-Coenzyme A (Walther y Farese Jr, 2012; Martines *et al.*, 2017). The two removed atoms are transferred to NAD⁺ generating NADH+H⁺ (Kohan *et al.*, 2015).

Finally thiolase divides C1 and C2 from 3-ketoacyl-Coenzyme A, releasing acetyl-Coenzyme A (Martines *et al.*, 2017), this shortens the two-carbon acyl-Coenzyme A chain, requiring another Coenzyme A, to finish the newly shortened molecule (Kong *et al.*, 2017). These steps are repeated until leaving a four-carbon acyl-Coenzyme A, where the four steps are repeated, only that instead of releasing one acetyl-Coenzyme A two are released (Civeira *et al.*, 2013).

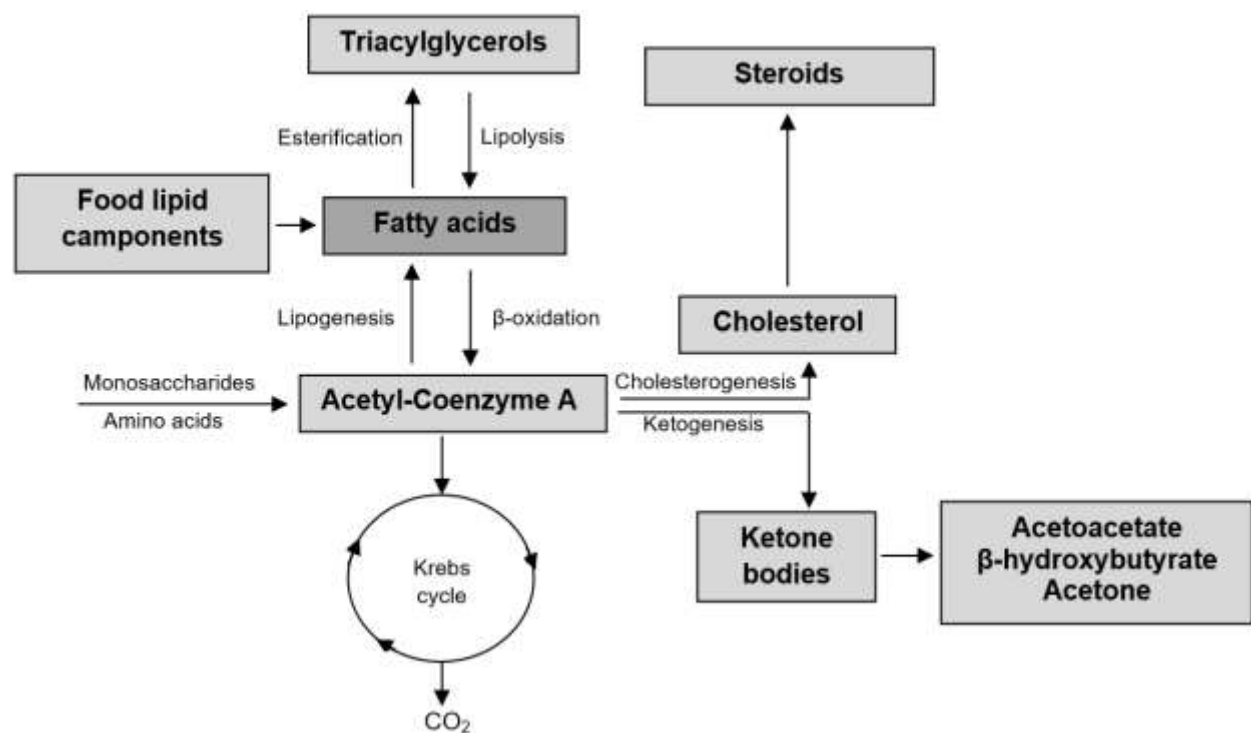


Figure 5. General metabolism of lipids

Source: synthesized information of (Du *et al.*, 2018)

When it comes to an odd fatty acid the penultimate repeat leaves a five-carbon fatty acyl-Coenzyme A and it undergoes the previous four steps, but the final two steps give one molecule of acetyl-Coenzyme A and one molecule of propionyl- Three carbon coenzyme A (Houten y Wanders, 2010). Acetyl-Coenzyme A as a product of the β -oxidation of fatty acids, can have three destinations: a) enter the Krebs cycle to oxidize to CO_2 and H_2O for energy release (Fukao *et al.*, 2014; Panov *et al.*, 2014); b) serve as a precursor for the synthesis of COL and other steroids (Walther y Farese Jr, 2012), and c) participate in ketogenesis (Watts y Ristow, 2017). The ketone bodies acetoacetate (**AcAc**), β -HBA and acetone (Garzón y Espinosa, 2018), serve as a substrate for the production of ATP (McFadden, 2020). They are synthesized in the liver, in low concentrations, but when intracellular $\text{C}_6\text{H}_{12}\text{O}_6$ decreases, their synthesis rises (Norris *et al.*, 2016).

Ketogenesis takes place in the mitochondrial matrix (Fukao *et al.*, 2014). When hepatic glycogen reserves decrease, the activity of carnitine palmitoyltransferase is stimulated, causing the transport of AGNE into the hepatic mitochondria (Walther y Farese Jr, 2012), where a series of successive β -oxidations is carried out, leading to the formation of acetyl-Coenzyme A (McFadden, 2020). This molecule is combined with oxaloacetate for its entry into the Krebs cycle (García *et al.*, 2015). If this oxidation is complete, CO_2 and hydrogen atoms will be released, which will donate their electrons to carry out oxide reduction reactions, which will culminate in the formation of H_2O and ATP (McFadden, 2020).

If oxaloacetate is reduced by acetyl-Coenzyme A, it accumulates within the hepatic mitochondria (Walther y Farese Jr, 2012); reason why two acetyl-Coenzyme A molecules react to form acetoacetyl-Coenzyme A, catalyzed by thiolase (Fukao *et al.*, 2014). Acetoacetyl-Coenzyme A binds with another acetyl-Coenzyme A molecule to form β -hydroxy- β -methylglutaryl-CoA, catalyzed by 3-hydroxy-3-methylglutaryl-CoA synthase (Norris *et al.*, 2016). Finally, the molecule is metabolized in AcAc (figure 5) and leaves the mitochondria to the cytoplasm, where it can be reduced in β -HBA or decarboxylated, up to acetone (García *et al.*, 2015).

Amino Acid Metabolism in Ruminants

The metabolism of aa involves transamination and deamination (Dong *et al.*, 2016), necessary reactions for the anabolism and catabolism of proteins (Golshan *et al.*, 2019). The aa Arg, histidine (**His**), isoleucine (**Ile**), leucine (**Leu**), lysine (**Lys**), methionine (**Met**), phenylalanine (**Phe**), threonine (**Thr**), tryptophan (**Trp**) and valine (**Val**), are mostly produced by ruminal fermentation (Zhou *et al.*, 2019). The aa are composed of an amino group ($-\text{NH}_2$) and a COOH group; in addition to an R side chain, which gives them hydrophilic, hydrophobic, acidic, basic and aromatic properties (Rostom y Shine, 2018). Transamination is carried out by aminotransferases, the $-\text{NH}_2$ group is transferred from an acidic aa to a ketoacid aa (Zhou *et al.*, 2019; Batista *et al.*, 2016). Aminotransferases are located in the cytoplasm and mitochondria, having two types of specificity: I) the type of aa that donates $-\text{NH}_2$ (Emery, 2015) and II) the keto acid that accepts $-\text{NH}_2$ (Dong *et*

al., 2016). Although enzymes vary depending on the type of aa they bind, most use glutamic (**Glu**) as a $-NH_2$ donor (Rostom y Shine, 2018).

These reactions require the pyridoxal phosphate cofactor (**PLP**) (Witus *et al.*, 2013). In oxidative deamination the aa lose the $-NH_2$, a reaction catalyzed by glutamate dehydrogenase (Dong *et al.*, 2016). The resulting carbon skeletons are degraded to one of seven possible metabolic products: acetyl-Coenzyme A, acetoacetyl-Coenzyme A, $C_3H_3O_3$, ketoglutarate, succinyl-Coenzyme A, fumarate, or oxaloacetate (Rostom y Shine, 2018). The aa's that degrade from acetyl-Coenzyme A to acetoacetyl-Coenzyme A are known as ketogens (Lys and Leu) (Batista *et al.*, 2016). The carbon skeletons of glycogenic aa degrade to $C_3H_3O_3$ or a Krebs cycle intermediate, but can also be converted to $C_6H_{12}O_6$ by glycogenesis (Emery, 2012). The NH_3 resulting from the deamination of the aa (figure 6) is transported to the periportal hepatocytes to participate in ureogenesis (García *et al.*, 2014).

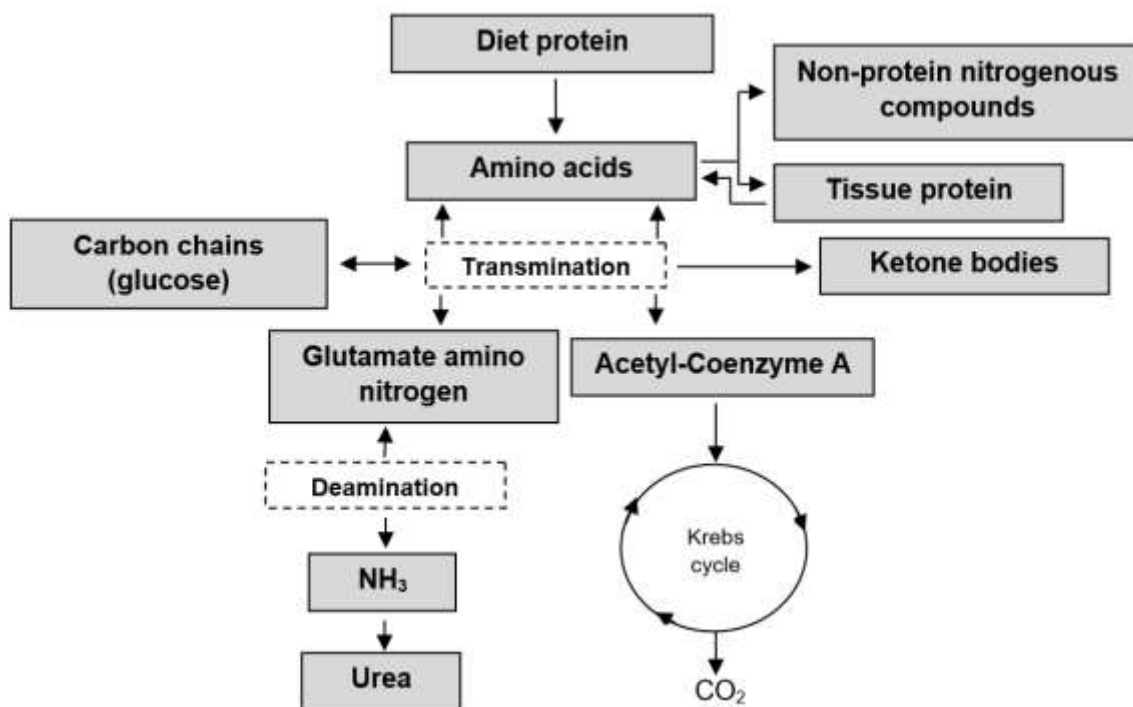


Figure 6. General metabolism of amino acids

Source: synthesized information of (Golshan *et al.*, 2019)

CONCLUSION

The scientific elements presented on anabolism and catabolism of nutrients show that intestinal absorption of glucose in ruminants is limited. Therefore, the ruminal microbiota plays an important role in the transformation, assimilation, and synthesis of each of the biochemical monomers; elements of vital importance in glycogenesis, proteogenesis, ureogenesis, lipogenesis and ketogenesis; metabolic processes that confer information on alterations and homeostatic adjustments in ruminants.

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