Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.20.003401

Urea Metabolism and Recycling in Ruminants

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ARTICLE INFO

Received: May 20, 2019

Published: July 29, 2019

Citation: Getahun D, Alemneh T, Akeberegn D, Getabalew M, Zewdie D. Urea Metabolism and Recycling in Ruminants. Biomed J Sci & Tech Res 20(1)-2019. BJSTR. MS.ID.003401.

Abbreviations: AA: Amino Acids; MCP; Microbial Crude Proteins; GIT: Gastrointestinal Tract; RFC: Ruminally Fermentable Carbohydrate; VFA: Volatile Fatty Acids; IIP : Indigestible Intake Protein; AHA: Acetohydroxamic Acid; PPD: Phosphoric Phenyl Ester Diamide; NBPT: N-(n-butyl) Thiophosphoric Triamide

Abstract

The major sources of nitrogen (N_2) in the diet of mammals are amino acids and peptides derived from ingested proteins. The immediate end product of mammalian protein catabolism is ammonia, which is toxic to cells if allowed to accumulate. Therefore, amino acids are broken down in the liver into urea, which is used as non-protein nitrogen in the rations of ruminants as an economical replacement for feed proteins. Urea transferred from the blood to the rumen is also an important source of nitrogen for rumen microbial growth. Mammals cannot break down urea, which is traditionally viewed as a simple waste product passed out in the urine. However, urea from the bloodstream can pass into the gastrointestinal tract, where bacteria expressing urease cleave urea into ammonia and carbon dioxide. The bacteria utilize the ammonia as a nitrogen source, producing amino acids and peptides necessary for growth. Interestingly, these microbial products can be reabsorbed back into the host mammalian circulation and used for synthetic processes; because of this reason, urea has commonly become an accepted ingredient in the diets of ruminants. Therefore, this review focuses on urea metabolism and recycling in ruminants.

Keywords: Urea; Metabolism; Ammonia; Urea N_2; Urea Recycling; Ruminants

Introduction

Urea and ammonia, in addition to amino acids (AA), peptides and microbial crude proteins (MCP), play an important role in nitrogen digestion and metabolism in ruminants. Also, urea could be used to replace a portion of dietary protein in ruminants [1]. Thereafter, some studies were conducted on the use of NPN in ruminant diets. During the 1970s and 1980s, multiple studies were conducted on the utilization of urea as a replacement for protein in ruminant diets, especially its effect on dry matter intake [2], rumen fermentation [1,3] milk yield and reproduction-related parameters [4,5]. Ruminants can utilize non protein nitrogen as a dietary protein source via their rumen microorganisms [6].

In most mammalian species, a large amount of endogenous urea-N is excreted via the urine. However, ruminants have evolved a mechanism that allows constant recycling of urea-N to the gastrointestinal tract (GIT), particularly to the rumen, where urea-N can be used as a source of N for microbial protein, which is the major contributor to the metabolizable protein supply to the small intestine. Urea-N recycling to the GIT and its utilization for anabolic use is influenced by several dietary and ruminal factors. Major dietary factors which regulate the proportion of hepatic urea output returning to the GIT and its subsequent fate are: dietary N concentration and N intake [7,8]; total dry matter intake [9]; feed processing [10-12]; oscillating dietary N levels [13] and amount as well as frequency of feeding dietary N that is degraded in the rumen [14,15]. In juxtaposition with dietary factors, ruminal factors such as ruminal NH3-N concentration, ruminal bacterial urease activity, ruminally-fermentable carbohydrate (RFC), ruminal concentrations of volatile fatty acids (VFA) and CO_2, and ruminal P^H also play a significant role in trans-epithelial movement of blood urea-N into the rumen [10]. So, the objective of this review is to assess the metabolism and recycling of urea in the ruminants.

Literature Review

Ammonia Production and Ammonia Toxicity

Usually, ruminants are much less efficient than no ruminants in utilizing high quality dietary proteins. A dominant feature of N Digestion and metabolism is microbial conversion of some dietary protein to NH_3. In ruminants, ammonia is generated by amino acids obtained from the diet, from catabolism of glutamine by enterocytes, or from peripheral tissues such as skeletal muscle. In mammals, at least 20 metabolic reactions generate ammonia, with the glutaminase, glutamate dehydrogenase and purine nucleo-tide cycle pathways producing most of the ammonia [16]. Ammonia generation in the gut results from two main processes: one is microbial degradation of nitrogenous compounds within the gut lumen; the other is microbial hydrolysis of urea passing across the gut wall from the blood and intestinal fluids [3].

The primary source of NH_3 within the rumen is dietary protein, except for ruminants consuming diets very low in protein. The UIP and indigestible intake protein (IIP) usually pass to the duodenum without affecting NH_3 production in the rumen. Degradable dietary NPN can be converted rapidly and quantitatively to NH_3 dissolved nucleic acids in the rumen are also degraded extensively by rapid action of bacterial peptidases and deaminases to produce NH_3 [17] Much of the daily ammonia load is derived from the catabolism of amino acid obtained from dietary proteins. In animals with high protein intake, 10% to 15% of the protein is delaminated and used for energy, with resultant ammonia production [18]. Urea recycling is significantly related to NH_3 production and absorption in the gastrointestinal tract (GIT) of ruminants. All NH3 absorbed from the rumen epithelium, small intestinal mucosa, and large intestinal mucosa travels via the portal vein to the liver; body tissue NH_3 also enters the liver. Liver metabolism has a central role in the integration of body N metabolism. Ammonia in the liver is detoxified by conversion to urea, urea can then is recycled directly into the rumen, small intestine, or large intestine; it can enter the rumen in saliva, be excreted by the kidney, or be secreted in milk or sweat [19].

Metabolism of Urea in the Liver

Under normal physiological and nutritional conditions, NH_3 absorbed into the portal vein is efficiently extracted by the liver and detoxified by conversion to urea or glutamine. Over a wide range of portal NH3 concentrations and on a variety of diets, the liver is able to extract 70 to 95% of portal NH3. As a result, hepatic NH_3 removal is on average slightly higher (4%) than portal absorption [17]. The structure and function of the liver attests to the importance of removing potentially toxic NH_3 from blood of ruminants as well as other mammals. The enzymes of the ornithine cycle and enzymes catalyzing transamination reactions are structurally oriented in mitochondria and cytosol of per portal and per venous hepatic cells to form urea from NH_3 absorbed from the gut and to use glutamine synthesis as another pathway to remove essentially all NH_3 from hepatic portal blood (Figure 1). Per portal cells remove NH_3 from hepatic portal blood and use their enzymatic machinery to synthesize urea. The specialty of the perivenous cells is production of glutamine through glutamine syntheses, thereby providing another opportunity to remove NH_3 from circulation before blood enters the hepatic veins and subsequently general circulation. This two-stage NH_3 removal system integrates with other systems, including gluconeogenesis, regulation of acid-base balance, and interorgan N shuttles to derive the best metabolic control of substrate and product balances, nutrient supplies, and nutrient needs of the organism [20].

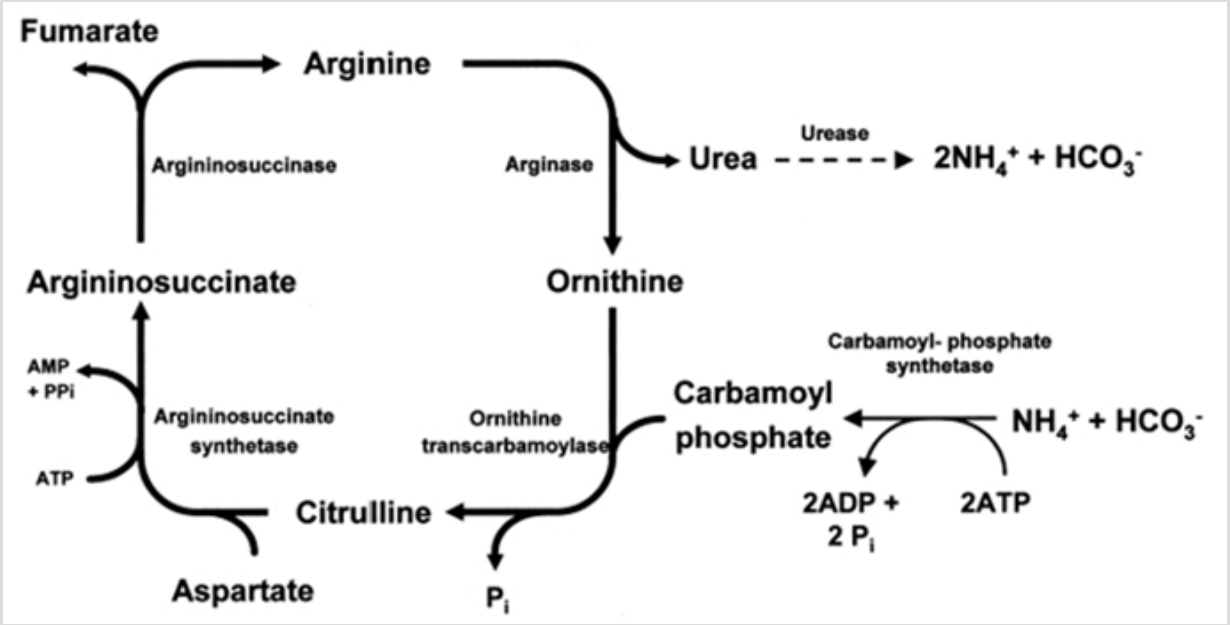

Figure 1: Urea Cycle in the Liver of Ruminants [21].

Rumen Ureolytic Bacteria

Rumen ureolytic bacteria play an important role in dietary urea hydrolysis, for they produce ureases that catalyze the breakdown of urea to ammonia (NH_3) and carbon dioxide [21, 22]. In the rumen, the ammonia can be assimilated by many rumen bacteria for the synthesis of microbial proteins [22]. However, the efficiency of urea N utilization in ruminants is low and this is attributed to the rapid hydrolysis of urea to NH3, which occurs at a higher rate than NH_3 utilization by rumen bacteria [23]. Due to the difficulty in cultivating rumen bacteria, only a small number of bacteria have been isolated [24]. The lack of sufficient understanding of the ruminal microbiome is one of the major knowledge gaps that hinder effective enhancement of rumen functions [25]. In addition, limited information about rumen urea-degrading bacteria makes regulation of the urea hydrolysis rate by targeting predominant ureolytic bacteria difficult.

Urea Transport

Urea transport Across the Rumen Epithelium: Urea produced in the liver is transferred across the rumen wall from the blood and then it is hydrolyzed to ammonia by resident bacteria [26]. As is already known, urea transport across the ruminant wall is mediated via urea transporters in the epithelium membrane [27]. These transporters allow the passage of urea across cell membranes, down a concentration gradient [28]. Facilitative urea transporters are derived from the UT-A and UT-B genes [29]. UT-B mRNA or protein expressions have been characterized in the rumen epithelium [30]. In the study of Coyle et al. [31], UT-B transporters were identified to be specifically localized to certain regions of tissue in the bovine gastrointestinal tract. Hepatic urea-N synthesis has two fates i.e., it is either excreted in the urine or is recycled back to the GIT via salivary secretions or by the direct transfer across the epithelial tissues of the digestive tract [32]. All mammalian species have the mechanism of urea-N recycling to the GIT. However, in ruminants the amount of urea-N recycled to the GIT (as a proportion of total hepatic urea-N output) varies between 29 to 99%, which is much greater compared to non-ruminants (15 to 39%) [33]. Animals utilize the released urea-N in a number of ways. In sheep, 30-50% of the urea that enters the digestive tract is returned to the host as ammonia, whereas this value is 25-40% for cattle [26]. The ammonia produced by urea hydrolysis is directly reabsorbed passively, independent of ionic concentrations, from both the rumen and the post-ruminal gut, particularly the caecum and large intestine. Approximately 20% of ruminal ammonia flux in sheep is derived from urea-N rather than ingested N [34].

Urea-N Recycling to the GIT: After synthesis, urea-N may either enter the gastrointestinal tract (GIT) or be excreted in the urine via the kidneys [5]. Urea-N that enters the rumen is able to be utilized by the microbial population and thereby improve whole animal N utilization. The quantity of urea-N that enters the GIT (GER) varies widely across and among species. Values of GER: N intake ranged from 0.19 to 0.80 among species and physiological status, with no apparent patterns observed among them (Figure 2). Urea-N recycling to the GIT occurs in all mammals; however, the magnitude of urea-N recycling is much greater in ruminants. Data from a variety of studies indicate that hepatic urea-N synthesis may be as high as digestible N intake (33 to 99%) and often exceeds digestible N intake [33]. Urea enters the ruminant gut by several routes. Although urea secreted in saliva accounts for between 10 and 40% of ruminal urea entry, the majority of urea enters across the gastrointestinal tract wall particularly across the ruminal epithelium. There is also a minor inflow in the bile secretion and pancreatic juice [35].

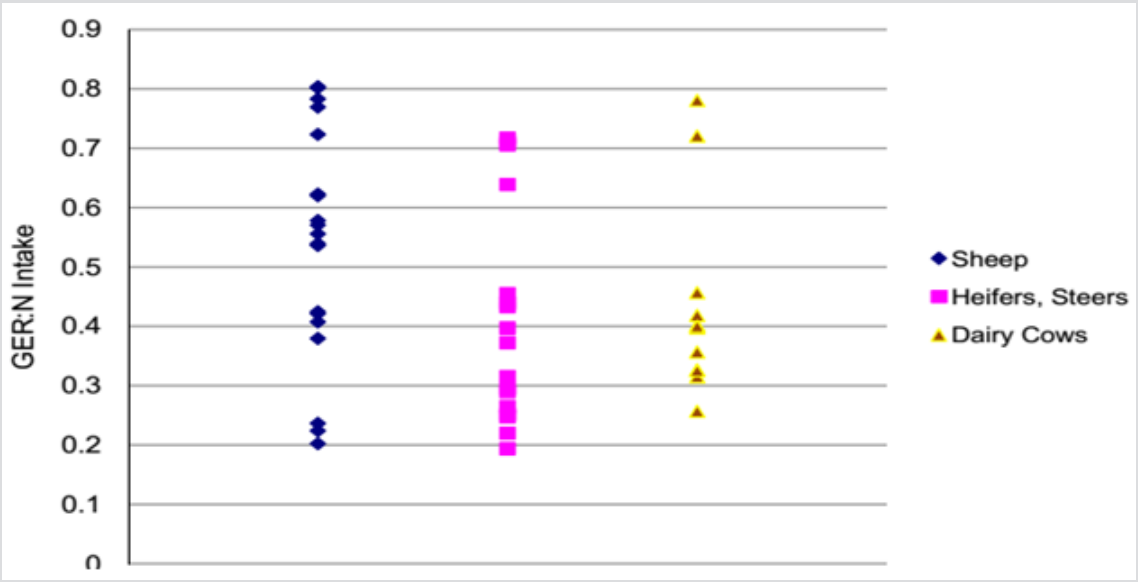

Figure 2: Gastrointestinal urea-N entry rate (GER) as a proportion of N intake in sheep and cattle studies [33].

However, the relative contributions of these routes can vary enormously depending on a complex interaction of factors, including the composition of diet ingested. For example, in cattle fed a concentrate diet, saliva secretion accounted for 17% of the total gut entry of urea, whereas in cattle fed a forage diet this value increased to 36% [26]. In high and rapidly growing ruminants, urea-N recycling to the GIT is so important that it can increase the N availability to the GIT from 43 to 130% [26]. Total urea synthesis in the liver can be as high as 33 to 99% of N intake. Of that total endogenous hepatic urea-N production in the liver, 1 to 71% of urea-N is excreted in the urine and about 29 to 99% enters the GIT. In the GIT 16 to 70% of urea-N (as a proportion that enters the GIT) is utilized for anabolic purposes and 3 to 21% is lost in feces. Unutilized urea-N (i.e., NH3-N) is returned to the ornithine cycle (17 to 80% of urea-N that enters GIT) for urea synthesis. The data depicted in this figure are obtained from urea-N kinetic measurements obtained from intra-jugular infusion of 15N15N-urea [36].

Urea Entry into the Rumen: Available data from literature [10,34] shows that between 27 to 60% (combined salivary contributions and transfer across the rumen wall) of the GIT entry is to the rumen. The quantity of urea-N transfer to different sections of the GIT is regulated by characteristics of the ruminant diet. Huntington [11] demonstrated that in steers fed high concentrate diets, up to 95% of urea-N (as a proportion of urea-N entry to the GIT) enters the rumen, as compared to 62.5% in steers fed high forage diet. Urea-N can enter the rumen via direct transfer of blood urea-N across the ruminal wall or via salivary secretions. Salivary urea-N entry to the rumen calculated as difference between total splanchnic flux and urinary excretions rate as a percent of total hepatic urea-N production represented 72% in steers fed high forage diets as compared to 21% in those fed high concentrate diet [11]. High roughage diets stimulate rumination, thus increasing the flow of salivary secretions to the rumen. Reports from other studies also show that salivary flow of urea-N into the rumen as a percent of total urea-N entry to the GIT was 36% in forage-fed [17] and 16% in concentrate-fed [37] ruminants. Recently, Ludden et al. [38] showed that UT-B proteins are present in the parotid gland in sheep and may be involved in the facilitated carrier-mediated transfer of urea-N into the saliva.

Urea Entry into the Small and Large Intestine: In ruminants, up to 70% of the total portal-drained viscera flux of urea can enter post-stomach (small intestine) compartments [26] of which up to 90% of total portal-drained viscera flux of urea is to the mesenteric-drained viscera in animals fed high fiber diets [11] as compared to only 19% in animals fed high concentrate diets [32]. However, most of the urea-N that enters post-stomach compartments is returned back to the ornithine cycle as NH3 for re-synthesis of urea [26]. Small amounts of urea-N are recycled to the hind gut (cecum and colon) and, even though bacteria residing in the hind gut utilize recycled urea-N for protein synthesis, because there are no mechanisms for digestion and absorption of microbial protein formed in the hind gut, it is eventually lost in the feces [33].

Factors Affecting Urea Recycling

All factors that influence the production, absorption, and transfer of NH_3 and urea will affect urea recycling in ruminants. Kennedy and Milligan [10] reported that urea transfer to the rumen was inversely related to the rumen NH_3 concentration and suggested that the NH3 concentration was a factor regulating urea entry into the rumen. There was a marked reduction of urea transfer to the rumen when the ruminal NH_3 concentration was elevated by continuous NH_3 infusion into it. Tracer studies have indicated that a supplemental energy source such as grain, starch, or dried beet pulp, significantly increased endogenous urea degradation in the gastrointestinal tract. It is possible that the rumen was the site of increased degradation because Kennedy and Milligan, [10] reported that dietary sucrose greatly enhanced the rate of transfer of urea to the rumen. On the other hand, urea transfer from blood to the GIT might not be controlled by the urea concentration in plasma alone. In sheep and cattle, the upper limits of the blood urea concentration above which urea transfer was no longer linearly related to plasma urea concentrations were 6.0 mm and 4.0 mm, respectively. Elevation of plasma urea above these concentrations did not further increase rumen NH_3. Norton et al. [39] found that transfer of urea into the post-ruminal tract is correlated with both plasma urea concentration and its production rate.

Inhibition: Increasing intraruminal ammonia concentration decreases the urea flux across the rumen wall [40]. According to Remond et al. [41], ammonia absorption may be responsible for reducing urea flux. The effect of ammonia on urease activity is long term [42] rather than short term, and the mechanism by which ammonia regulates the trans-epithelial flux of urea during short-term variations is not yet known.

Impact of Animal Factors on Urea Recycling: Production of urea is largely a substrate-driven process. Thus, animal productivity can impact urea recycling by impacting how much N is available for urea synthesis. When cattle use more N for productive purposes (i.e., growth or lactation), less N are available for urea synthesis and therefore less urea are recycled to the gut. Bailey [43] compared urea recycling in forage-fed steers weighing 208 and 391 kg; the larger steers were physiologically more mature and deposited less N in tissue proteins than the younger steers. The more mature cattle had greater urea synthesis and greater urea recycling than the younger cattle that deposited more tissue protein. Thus, body protein utilization impacts urea recycling.

Urease Inhibitors in Ruminants: Urea hydrolysis to ammonia in the rumen is very rapid, which can override its utilization by the ruminal microorganisms and lead to ammonia toxicity and wastage of nitrogen of feeds. Therefore, slowing down the urea hydrolysis may reduce ammonia loss and improve urea utilization. Coated urea or slow release urea products as protein supplements could constantly supply ammonia to ruminal microorganisms for their growth without the potential toxicity associated with feed-grade urea [44], which may also improve nutrient utilization for

low-quality forages and reduce plasma ammonia concentrations [45]. Another strategy, which has been explored for many years to decrease the urease activity in the rumen, is the use of urease inhibitors (Table 1). A number of urease inhibitors such as acetohydroxamic acid (AHA), phosphoric phenyl ester diamide (PPD), N- (n-butyl) thiophosphoric triamide (NBPT), boric acid, bismuth compounds and hydroquinone decrease ureolytic activity. However, some of these compounds pose potential risks to animal and human health, thus precluding their use in production. These inhibitors usually work very well when tested *in vitro* [46-49].

Table 1: Different urease inhibitors used to inhibit ureolytic bacteria and urease activity in the gastrointestinal tract of livestock animals.

Urease Inhibitor	System	Response	Reference
Phenylphosphoryldiamidate (1 g/day) infusion into the rumen	Sheep	a) Reduced urease activity by > 98%, rumen ammonia concentration by 40%, urea degradation by 70%. b) Increased in plasma urea concentration and nitrogen retention. c) No effect on urea excretion	[6]
Phenylphosphoryldiamidate (1 g/day) infusion into the abomasum	Sheep	a) Decreased urease activity by 40% b) No effect on urea metabolism.	[6]
N (n-butyl) thiophosphoric triamide (0.125-4 g/day)	Sheep	a) Decreased ruminal urease activity and ammonia linearly and increased ruminal urea linearly b) Inhibitor activity reduced with day c) No effect on dry matter or fiber digestibility, but nitrogen digestibility. d) Increased urinary nitrogen excretion and decreased nitrogen retention linearly	[38]
Vaccination, UreC proteins of *H. pylori*	Cow	a) Decreased urease activity in rumen fluid by 17%. b) Lowered ureolysis and ammonia concentration in the ruminal fluid.	[47]
Vaccination, jack bean urease	Calves	a) Increased growth rate and feed efficiency	[48]

Conclusion

Urea is one of the major non-protein nitrogen feeds for ruminants and the optimal utilization of urea in feed can alleviate to some extent the cost of dietary protein. Urea is hydrolyzed quickly by ureolytic bacteria in the rumen. The ability of the liver to detoxify NH3 to urea appears to be similar in ruminant and non-ruminant species, the principal difference being that the production of NH_3 by foregut fermentation in ruminants is extremely variable and dependent on feed sources, whilst in non-ruminants, NH_3 is produced in the hindgut and, therefore, absorption into the portal vein is affected far less by diurnal feed cycles. Despite the high rates of uptake from the gut, which result from rapid fermentation of soluble N in forage diets, the ruminant liver is extremely adept at detoxifying NH_3 to urea. However, there is evidence to suggest that NH_3 detoxification to urea imposes a metabolic 'cost' in terms of amino acid deamination. This could explain observations of poor N retention in forage-fed ruminants, although further specific metabolic studies are required to identify mechanism which could explain this interaction of NH_3 with amino acid metabolism. Also urea that is produced in the rumen is circulating in to gastro intestinal tract of ruminants.

Acknowledgment

Authors would like to thank Debre Berhan University Librarians, Staffs and the Community in general for their logistic and material supports that greatly aid for the success of this work.

Conflict of Interest

Authors declare that no conflicting of interests.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.20.003401

Tewodros Alemneh. Biomed J Sci & Tech Res