Conference: Hepatic Metabolism of Organic Acids in Ruminants

Metabolism of Nitrogenous Compounds by Ruminant Liver[1]

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ABSTRACT Ruminants absorb substantial amounts of ammonia nitrogen and very little glucose. Ammonia absorbed is removed by the liver and converted to urea, which can be recycled to the digestive tract and add to the pool of ammonia absorbed. When ammonia absorption and liver urea production are increased by changes in nitrogen intake, an associated increase in liver α-amino nitrogen removal has been observed. Reasons for the increase in liver removal of amino acids with greater ureagenesis are uncertain, but the aspartate/glutamate requirement of ureagenesis and the complex relationships between ureagenesis and the tricarboxylic acid cycle, glucogenesis, liver energy metabolism and redox state all may be involved. Amino acids represent potential sources of carbon for liver glucogenesis and precise reckonings of the contributions of amino acid carbon to glucogenesis are needed for ruminants fed differing diets. There is evidence for the involvement of peptides in liver nitrogen exchanges and amino acids in peptides represent a potential source of carbon for glucogenesis and nitrogen for ureagenesis. A number of endocrine factors have an impact on liver nitrogen metabolism in ruminants. Growth hormone decreases liver urea release and increases liver glutamate release. J. Nutr. 122: 850–854, 1992.

INDEXING KEY WORDS:

• *ruminants* • *liver* • *amino acids*
• *ammonia* • *urea*

Liver metabolism has a central role in the integration of body nitrogen metabolism. The liver is positioned vascularly to receive all blood draining tissues of the portal-drained viscera (PDV),[3] which include the digestive tract, pancreas, spleen and mesenteric fat. Therefore, liver metabolism dictates the availability of many nutrients absorbed to other body tissues (1).

Ruminants absorb substantial amounts of their dietary nitrogen as ammonia. For many diets, ruminants absorb more nitrogen as ammonia than as α-amino nitrogen (2). The liver removes and detoxifies this ammonia, primarily by converting it into urea, which is released into the vena cava. Although much of this urea is excreted in the urine, from 40 to 60% is excreted into the lumen of the digestive tract via saliva or direct transfer from blood (3). Urea transferred into the digestive tract can be metabolized by microbial urease, forming ammonia, which can be reabsorbed or used for microbial synthesis of amino acids. Ammonia also arises from the catabolism of amino acids, nucleic acids and other nitrogenous compounds (1) and transamination of amino acids contributes nitrogen to ureagenesis via glutamate and aspartate.

Thus, there is an inherent cycling of nonprotein nitrogen between the digestive tract and liver, which involves and affects the metabolism of other nitrogenous compounds in ruminants. Consequently, much of this review will focus on the metabolism of ammonia by liver and the process of ureagenesis.

A second aspect of liver nitrogen metabolism in ruminants results from the constant demand of liver glucogenesis for glucose precursors. Ruminants absorb little, if any, dietary carbohydrate as glucose; therefore, liver synthesis must meet essentially all body glucose requirements. Amino acids represent a critical source of carbon for glucogenesis in ruminant liver (4). The

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[3] Abbreviations: PDV, portal-drained viscera; GRF, growth-hormone–releasing factor.

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processes of glucogenesis and ureagenesis are integrated via the tricarboxylic acid cycle and their requirements for specific amino acids and oxaloacetate (5).

Much of the data described in this paper was obtained by using multicatheterization procedures, which have been described in detail for sheep (6) and cattle (7). By surgically implanting catheters in the visceral vasculature, measurements of venous-arterial concentration difference and blood flow can be obtained and combined mathematically to calculate net uptake or release of specific nutrients by the PDV and liver. Together, these tissues form a functional unit, often called the total splanchnic tissues. Net release of a nutrient by the total splanchnic tissues represents the amount of that nutrient available to the rest of the body after absorption and metabolism by the digestive tract and liver.

The intense metabolic activity of liver tissues is demonstrated by its oxygen consumption. In growing heifers, liver oxygen uptake accounted for 18–26% of whole-body oxygen consumption (8) yet likely only accounted for 1–2% of body tissue mass (1). This disproportionate use of oxygen is due to a number of metabolic processes, which include protein synthesis and degradation, ureagenesis, the maintenance of ionic balance, futile cycles and mixed-function oxidase activity (9). Protein synthesis is a major route of amino acid utilization in the ruminant liver, and liver tissues account for from 9 to 13% of body protein synthesis in sheep and cattle (10, 11). In addition, amino acids provide oxidizable substrate to meet liver energy needs (1).

INTERORGAN AMINO ACID EXCHANGE

The most comprehensive data describing amino acid metabolism by the ruminant liver was obtained by using multicatheterization procedures by Bergman and colleagues (4, 6) who conducted a progression of studies in sheep that were usually fed alfalfa hay at maintenance intake. Their studies identified free amino acids that are major players in the interorgan exchange of carbon and nitrogen in ruminants. For the glucogenic amino acids alanine, glycine and serine, their net removal by liver was greater than or equal to their net absorption by PDV such that their total splanchnic flux was negative, representing the contribution of other body tissues to liver metabolic requirements and glucose synthesis (6). On a net basis, the liver removed arginine and released citrulline plus ornithine, whereas the opposite pattern was observed for kidneys. This interorgan cycling of these amino acids represents a spatial separation of the urea cycle, which allows the participation of extrahepatic tissues (4).

Liver tissues released glutamate, which was removed by hindlimb tissues, and removed glutamine, which was released by hindlimb tissues (6). This shuttle of glutamate and glutamine between liver and peripheral tissues provides a mechanism for transporting ammonia to the liver for detoxification via ureagenesis. In addition, both of these amino acids provide carbon for glucose synthesis. Similarly, alanine and glycine released by hindlimb and PDV tissues transport ammonia to the liver for detoxification and provides carbon for glucogenesis. Liver removal of the branched-chain amino acids leucine, isoleucine and valine was not as great as their net PDV absorption. The resulting net total splanchnic release of these amino acids was in part balanced by their removal by peripheral tissues (6).

Net flux rates of individual amino acids represent the summation of unidirectional, or true, rates of uptake and release by a tissue. By combining net flux measurements with the infusion of an isotopically labeled amino acid, unidirectional liver metabolism of individual amino acids can be described (12, 13). In sheep, net liver removal of glutamine was 2.6 times lower than unidirectional removal because of substantial unidirectional release of glutamine that was also occurring (4). One explanation for the simultaneous release and removal of glutamine by the total sheep liver may be liver heterogeneity. In rats, periportal hepatocytes remove glutamine and ammonia and release urea, whereas perivenous hepatocytes remove ammonia and release glutamine. Glutamine released by perivenous hepatocytes can recirculate to the liver and be used for ureagenesis in periportal hepatocytes (14). If the ruminant liver also exhibits this heterogeneity, this represents an intracellular cycling of glutamine that is additional to the interorgan cycling of glutamine already demonstrated (6).

Two aspects of the data published by Bergman and colleagues (4, 6) that must be considered when applying their data to other productive states are the use of near maintenance intakes and the inherently high crude protein content of alfalfa. Both of these factors could increase the utilization of amino acids by liver relative to other body tissues. At maintenance intake, absorption of amino acids relative to liver requirements could be lowered. In addition, the high rate of ammonia absorption in sheep fed alfalfa (15) could increase amino acid and energy requirements of ureagenesis.

DIET EFFECTS

Patterns of net amino acid metabolism by liver of cattle (16) are qualitatively similar to those reported for sheep; however, at production intakes, net liver removal of many amino acids was not as great as their net absorption by PDV, such that a net total splanchnic release was measured. The exception was glycine,

which was removed by total splanchnic tissues and released by the hindlimbs. In growing cattle, greater diet intake increased net PDV absorption and liver removal of α-amino nitrogen, but the increase in liver removal was less than the increase in PDV absorption, such that total splanchnic release increased with intake (17). Similarly, PDV absorption and liver removal of α-amino nitrogen increased in steers abomasally infused for 3 d with casein, but in this instance the increase in liver removal matched the increase in PDV absorption and therefore total splanchnic release did not change (18).

Responses of liver nitrogen metabolism to varying intake appear to occur in a matter of days. In rats, enzymes participating in liver nitrogen metabolism adapted to changes in abrupt, marked changes in protein intake in 2–8 d (19, 20). In beef cattle, responses of liver nitrogen metabolism to changes in intake of a concentrate diet were similar whether measurements were obtained 5 d (17) or 6 wk (22) after completion of stepwise changes in intake.

The most dramatic effect of dietary nitrogen manipulation on nutrient absorption in ruminants is the change in net PDV absorption of ammonia resulting from changes in rumen degradable protein intake (23). In beef steers fed alfalfa containing 17% crude protein or concentrate containing 12% crude protein at equal metabolizable energy intake, net PDV absorption of α-amino nitrogen was similar between the two diets, but net PDV absorption and liver removal of ammonia more than doubled when steers were fed alfalfa compared with concentrate. This increase in liver removal of ammonia resulted in a doubling of liver urea production and a threefold increase in liver α-amino acid nitrogen removal, such that total splanchnic release of α-amino nitrogen to other body tissues was markedly reduced. Similar trends were evident in beef heifers fed isonitrogenous diets differing in forage/concentrate ratio at equal metabolizable energy intakes (17). Heifers fed the high forage diet, which had a lower metabolizable energy density, consumed and digested more nitrogen. As a consequence of greater nitrogen digestion, heifers fed the high forage diet absorbed more ammonia and their livers produced more urea and removed more α-amino nitrogen than when fed the high concentrate diet (**Table 1**). In addition, the liver of heifers fed the high forage diet released less glutamate. Glutamate provides one nitrogen in urea via transamination of oxaloacetate to form aspartate and the formation of arginosuccinate via arginosuccinate synthetase (24). The requirement of glutamate in ureagenesis provides one explanation for the increase in liver removal of α-amino nitrogen when ureagenesis increased in these studies. A small part of the increase in α-amino nitrogen removal is accounted for by the decrease in glutamate release. In addition, transamination of amino acids may be required for the formation of glutamate and aspartate needed for ureagenesis.

TABLE 1

Net release (+) or removal (−) of blood nitrogenous compounds and oxygen by liver of beef heifers fed isonitrogenous diets containing 75% alfalfa or 75% concentrate at two intakes[1]

Item	75% Alfalfa diet		75% Concentrate diet		SEM
	Low	High	Low	High	
	mmol/h				
Ammonia nitrogen[ab]	−194	−353	−148	−260	31
α-amino nitrogen[ab]	−76	−172	−58	−130	16
Glutamate[b]	−3	7	8	15	7
Urea nitrogen[ab]	354	593	235	491	64
Oxygen[a]	−360	−607	−311	−598	47

[1] Diets contained 17.4% crude protein and were fed at 2-h intervals (adapted from ref. 17).
[a] Intake effect, $P < 0.01$.
[b] Diet effect, $P < 0.05$.

Increased utilization of α-amino nitrogen with increased ureagenesis may also relate to the shared requirements of glucogenesis and ureagenesis for oxaloacetate. Data of Krebs et al. (5) demonstrated that the addition of glucose precursors to culture media for rat hepatocytes increased urea formation from ornithine and ammonia in the presence of oleate. This was believed to be due to the oxaloacetate requirement for aspartate generation. If ureagenesis draws oxaloacetate from glucogenesis, then perhaps increased amino acid catabolism is required for oxaloacetate replacement. However, fumarate produced by the urea cycle can enter the tricarboxylic acid cycle and be used for oxaloacetate regeneration (24).

Another interaction between ureagenesis and the tricarboxylic acid cycle is the use of α-ketoglutarate for glutamate synthesis. Increased ammonia concentrations in the mitochondria can increase the synthesis of glutamate by glutamate dehydrogenase, thereby reducing the availability of α-ketoglutarate to the tricarboxylic acid cycle (25). In nonruminants, excess ammonia can be captured as glutamate or glutamine when the ability of the carbamoyl phosphate synthetase reaction to capture ammonia is exceeded (14). Equilibrium concentrations of glutamate, aspartate, oxaloacetate and α-ketoglutarate in the mitochondria and cytosol will be determined in part by redox states and the exchanges of these metabolites, their intermediates and reducing equivalents across the mitochondrial membrane (24). Liver concentrations of NADH and NADPH were lowered in sheep fed diets containing nonprotein nitrogen (26), which would limit glutamate synthesis by glutamate dehydrogenase.

Liver amino acid utilization may also support ureagenesis by providing a source of energy. When considered in and of itself, the urea cycle requires four high energy phosphate bonds. In dairy cattle, the reduced net energy available from high protein diets has been attributed to increased heat production resulting from urea production and recycling via the digestive tract (27, 28). However, Newsholme and Leech (24) account for the gain in ATP resulting from fumarate metabolism to oxaloacetate when calculating energy costs of ureagenesis, leaving the net cost at one ATP. In beef heifers fed and digesting differing amounts of nitrogen at equal metabolizable energy, greater liver urea production in heifers absorbing greater amounts of ammonia did not result in a significant increase in liver oxygen consumption (Table 1). This agrees with the accounting of Newsholme and Leech (24) but may also be attributable to counterbalancing changes in liver metabolism resulting from differences in diet composition. The true cost of increased ureagenesis and reasons for decreased energy availability in ruminants fed excess protein appears more complex than an increase in liver energy requirement per se and may relate to increased amino acid utilization or effects on glucogenesis and exchanges of carbon via the tricarboxylic acid cycle (26).

GLUCOGENESIS

It is known that amino acids contribute carbon to liver glucose synthesis, but precise measurements of the quantity of glucose carbon originating from amino acids is lacking. Many amino acids must enter the tricarboxylic acid cycle to be used for glucogenesis, therefore a loss of carbon as CO_2 accompanies their contribution to glucose. Although net rates of liver amino acid removal maximally accounted for 30% of liver glucose synthesis in sheep, isotopic measurements of carbon transfer from amino acids to glucose in the same sheep only accounted for 15% of liver glucose release (4). In cattle, net rates of glucose precursor removal by liver maximally account for 90–100% of liver glucose release, with amino acids contributing 12–16% (23). However, these maximal rates assume that all the carbon in these precursors appears in glucose released, which is unlikely. Similarly, liver removal of ammonia and α-amino nitrogen often fails to account for all the nitrogen in urea released by liver (Table 1). Sources of this urea nitrogen include nitrogen in amino acid side-chains, nucleic acids, protein degradation and peptides. There is evidence for interorgan transport of amino acids as peptides in ruminants (29, 30) and peptides would provide a source of carbon for glucogenesis and nitrogen for ureagenesis. Peptide hydrolases from the plasma membrane of rat liver cells have been described (31). In addition, the liver internalizes and degrades a number of large peptides such as insulin and glucagon (32).

REGULATION

Liver nitrogen metabolism is known to be affected by a number of hormones, but the role of endocrine factors in liver responses to diet and growth promotion need further investigation. In sheep, glucagon increases and insulin decreases liver removal of alanine and alanine use for liver glucogenesis (15, 33). In addition, liver removal of glutamine and other glucogenic amino acids is increased by glucagon (15, 34). Other hormonal regulators of liver nitrogen metabolism include catecholamines, glucocorticoids and growth hormone (34).

In a recent study, beef steers were injected with saline or growth-hormone–releasing factor (GRF) at two intakes (22). Injection of GRF doubled body nitrogen retention at both intakes. The increase in body nitrogen retention resulting from GRF injection was associated with decreased liver production of urea, decreased liver removal of ammonia (due to decreased PDV absorption), decreased liver removal of α-amino nitrogen and increased liver release of glutamate (**Table 2**). Hence, treatment with GRF reduced the cycling of nonprotein nitrogen between the PDV and liver. There were no effects of GRF treatment on liver metabolism of alanine, glutamine or the urea cycle intermediates. The increase in liver glutamate release may have resulted from decreased urea cycle activity and provides more glutamate for use by peripheral tissues. This observation agrees with data from heifers

TABLE 2

***Net release (+) or removal (−) of blood nitrogenous compounds by liver of beef steers injected with saline or growth-hormone–releasing factor (GRF) at two intakes of a concentrate diet*[1]**

	Low intake		High intake		
Item	Saline	GRF	Saline	GRF	SEM
			mmol/h		
Urea nitrogen[ab]	239	173	391	338	15
Ammonia nitrogen[ab]	−148	−127	−213	−181	11
α-amino nitrogen[ab]	−32	−11	−76	−69	3
Glutamate[ab]	18	23	24	31	2
Alanine[b]	−11	−13	−35	−37	4
Glutamine[c]	−1	−5	−24	−21	7

[1] The diet contained 16.6% crude protein and was fed at 2-h intervals (adapted from ref. 22).
[a] GRF effect, $P < 0.05$.
[b] Intake effect, $P < 0.05$.
[c] Intake effect, $P < 0.10$.

in which urea cycle activity was manipulated dietarily (Table 1). The decrease in liver removal of α-amino nitrogen also provided more α-amino nitrogen for use by peripheral tissues and may relate to the relationships between liver removal of α-amino nitrogen and ureagenesis observed in other studies (Table 1) (7). In hypophysectomized rats, growth hormone treatment also decreased liver ureagenesis and increased net liver release of glutamate without affecting liver metabolism of alanine or glutamine (35). Whether these responses are the result of direct effects of growth hormone elevation and subsequent endocrine, paracrine or autocrine responses on liver per se or are a result of increased nitrogen utilization in extrahepatic tissues and a reduction in surplus nitrogen availability is not certain.

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