

## Intestinal Mucosal Amino Acid Catabolism<sup>1,2</sup>

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**ABSTRACT** The small intestine is not only responsible for terminal digestion and absorption of nutrients, but it also plays an important role in catabolism of arterial glutamine and dietary amino acids. Most of glutamine and almost all of glutamate and aspartate in the diet are catabolized by small intestinal mucosa, and CO<sub>2</sub> accounts for 56–64% of their metabolized carbons. The small intestinal mucosa also plays an important role in degrading arginine, proline and branched-chain amino acids, and perhaps methionine, lysine, phenylalanine, threonine, glycine and serine in the diet, such that 30–50% of these dietary amino acids are not available to extraintestinal tissues. Dietary amino acids are major fuels for the small intestinal mucosa and are essential precursors for intestinal synthesis of glutathione, nitric oxide, polyamines, purine and pyrimidine nucleotides, and amino acids (alanine, citrulline and proline), and are obligatory for maintaining intestinal mucosal mass and integrity. Because intestinal amino acid catabolism plays an important role in modulating dietary amino acid availability to extraintestinal tissues, it has important implications for the utilization efficiency of dietary protein and amino acids in animals and humans. *J. Nutr.* 128: 1249–1252, 1998.

**KEY WORDS:** • intestine • amino acids • metabolism

The small intestine is the primary organ responsible for terminal digestion and absorption of dietary nutrients including protein and amino acids. Until the pioneering work of Windmueller and co-workers on glutamine utilization by rat jejunum (reviewed in Windmueller 1982), it was tacitly assumed that all dietary amino acids absorbed by the small intestinal mucosa entered the portal circulation intact and became available to extraintestinal tissues. Studies over the last two decades have demonstrated extensive catabolism of nonessential amino acids in intestinal mucosa (Burrin and Reeds 1997, Wu et al. 1996). In recent years, there has been growing recognition that catabolism dominates the first-pass intestinal utilization of dietary essential amino acids (Stoll et al. 1998b). The major objective of this review is to examine current views of intestinal mucosal amino acid catabolism and its implications for protein and amino acid nutrition.

### AMINO ACID CATABOLISM IN INTESTINAL MUCOSA

**Glutamine, glutamate and aspartate.** In a series of elegant studies, Windmueller and co-workers demonstrated extensive uti-

lization of arterial glutamine and luminal glutamine, glutamate and aspartate by rat small intestine (reviewed in Windmueller 1982). The small intestine of the postabsorptive adult rat extracts 25–33% of arterial glutamine in a single pass, which accounts for 30% of whole-body glutamine utilization. In contrast to glutamine, uptake of arterial glutamate and aspartate by the small intestine is not significant. However, intraluminally delivered glutamate and aspartate, like glutamine, are metabolized extensively by the small intestinal mucosa; 66, 98 and >99% of luminal glutamine, glutamate and aspartate (6 mmol/L for each) is catabolized in a single pass by rat jejunum, respectively (Windmueller and Spaeth 1975 and 1976). Similarly, 96 and 95% of enterally delivered glutamate is extracted in the first pass by the human splanchnic bed (Battezzati et al. 1995) and by porcine portal-drained viscera (PDV)<sup>3</sup> (mainly intestine) (Reeds et al. 1996), respectively. Thus, most of glutamine and almost all glutamate and aspartate in the diet do not enter the portal circulation and are not available to extraintestinal tissues (Battezzati et al. 1995, Stoll et al. 1998b).

The metabolic fate of glutamine, glutamate and aspartate and the activities of catabolizing enzymes have been quantified in rat small intestine (Windmueller 1982). Ammonia, citrulline, alanine and proline released by rat jejunum account for 37.9, 27.6, 24.4 and 7.2% of the metabolized glutamine nitrogen, respectively. In contrast to glutamine, there is little or no production of ammonia from glutamate and aspartate in the small intestine (Windmueller and Spaeth 1975 and 1976), suggesting a dominant role of transamination in their catabolism. In adult rat small intestine, CO<sub>2</sub>, lactate, alanine and glucose account for 56–64, 16–20, 4–8 and 2–10% of the total catabolized carbons of luminal glutamine, glutamate and aspartate, respectively (Table 1). Under conditions similar to a meal, oxidation of arterial glutamine, luminal glutamine plus glutamate plus aspartate, and luminal glucose accounts for 38, 39 and 6% of the CO<sub>2</sub> produced by rat small intestine, respectively (Windmueller 1982). About 75 and 65% of enterally delivered glutamate is oxidized to CO<sub>2</sub> in the first pass by human splanchnic bed (Battezzati et al. 1995) and by porcine PDV (Reeds et al. 1996), respectively. These results demonstrate that amino acids, rather than glucose, are the major fuel for the small intestinal mucosa.

Syntheses of purine and pyrimidine nucleotides and of glutathione represent physiologically important pathways for intestinal utilization of glutamine and aspartate and of glutamate, respectively; however, little quantitative data are available (Burrin and Reeds 1997). Reeds et al. (1997) reported that luminal glutamate, rather than glutamine-derived glutamate, was the preferential source of glutamate for glutathione synthesis in intestinal mucosa. This result suggests that the catabolism of intestinal glutamine and glutamate is highly compartmentalized.

**Serine and glycine.** Rat small intestine appears to contain negligible or low activity of serine dehydratase and serine aminotransferase and virtually no activity of the glycine cleavage system, but a significant amount of serine hydroxymethyltransferase (Kikuchi et al. 1980). The latter interconverts serine into glycine and generates N<sup>5</sup>,N<sup>10</sup>-methylene tetrahydrofolate for purine and pyrimidine synthesis, and is likely quantitatively important for high rates of protein synthesis and cell prolifera-

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<sup>3</sup> Abbreviations used: BCAA, branched-chain amino acids; NO, nitric oxide; PDV, portal-drained viscera; P5C, Δ<sup>1</sup>-pyrroline-5-carboxylate.

TABLE 1

*The metabolic fate of the carbons of luminal glutamine, glutamate, aspartate and arginine utilized by adult rat small intestine<sup>1</sup>*

	Gln	Glu	Asp	Arg
% of total catabolized amino acid carbons in product				
CO <sub>2</sub>	56	64	51	14
Lactate	16	16	20	—
Proline	5.8	4.1	1.7	13
Citrulline	4.4	3.2	1.1	17
Alanine	4.0	3.3	8.0	1.1
Ornithine	2.1	1.0	0.4	32
Glucose	2.4	—	10	—

<sup>1</sup> Adapted from Windmueller and Spaeth (1975 and 1976).

tion in intestinal mucosa (Burrin and Reeds 1997). Glutathione synthesis represents a physiologically important pathway for glycine utilization by small intestinal mucosa (Reeds et al. 1997). Stoll et al. (1998b) reported that 40 and 50% of dietary serine and glycine were extracted in the first pass by PDV of milk protein-fed pigs, respectively, and <20% of the extracted amino acids were utilized for intestinal protein synthesis. This result suggests that dietary serine and glycine may be substantially catabolized by small intestinal mucosa; however, direct evidence for their catabolism via pathways other than glutathione and nucleotide syntheses is lacking.

**Arginine.** There are marked developmental changes in intestinal arginine catabolism. Arginine catabolism in pig enterocytes (absorptive cells of the small intestine) is limited at birth and during the suckling period due to negligible arginase activity (Wu et al. 1996). This helps to maximize the output of arginine by the neonatal small intestine. Intestinal arginine degradation is markedly enhanced at weaning due to the induction of arginase (Wu et al. 1996), which is mediated mainly by a glucocorticoid-dependent mechanism (Flynn and Wu 1997). As such, urea is synthesized from extracellular and intramitochondrially generated ammonia and from arginine in enterocytes of weaned pigs but not in cells of preweaning pigs (Wu 1995). This novel finding challenges the traditional view that the liver is the only cell type capable of ureagenesis.

In adult rats, 40% of the luminal arginine absorbed by intestinal mucosa is catabolized in a single pass, and the remaining 60% of the absorbed arginine enters the intestinal venous blood intact (Windmueller and Spaeth 1976). In adult humans, 38% of dietary arginine is removed in the first pass within the splanchnic bed, and most of the arginine utilization is accounted for by the small intestinal mucosa (Castillo et al. 1993a). These results indicate that substantial amounts of dietary arginine are not available to extraintestinal tissues. In milk protein-fed piglets, there is output of arginine by PDV (Stoll et al. 1998b), which results from the balance between arginine synthesis and catabolism by intestinal mucosa.

Intestinal mucosal arginine degradation is initiated primarily by type II arginase and to a much lesser extent, by nitric oxide (NO) synthase (Wu et al. 1996). In enterocytes, type II arginase is located in both the cytosol and mitochondria, and arginine-derived ornithine is converted mainly into proline by ornithine aminotransferase and  $\Delta^1$ -pyrroline-5-carboxylate (P5C) reductase (Davis and Wu 1998). In these cells, proline, ornithine, citrulline and CO<sub>2</sub> account for 56, 37, 4 and 1% of the metabolized arginine carbons, respectively, and polyamines and NO are quantitatively minor products of arginine (Wu et al. 1996). In rat jejunum, ornithine is the major product of

arginine and there is substantial oxidation of arginine to CO<sub>2</sub> (Table 1). Castillo et al. (1993b) reported that, in healthy adult humans, only 0.34% of the dietary arginine taken up in the first pass within the splanchnic bed was utilized for NO synthesis, which contributed to 16% of the total daily endogenous NO production.

**Proline.** Wu (1997) recently demonstrated the presence of a relatively high activity of mitochondrial proline oxidase in enterocytes from 0- to 58-d-old pigs and in rat small intestine, in contrast to the view that this enzyme was absent from the gut of postnatal rats (Wakabayashi 1995). Relatively large amounts of ornithine, citrulline and arginine are synthesized from proline by pig enterocytes in a concentration-dependent manner, and account for ~80–90% of the metabolized proline carbons (Wu 1997). Similarly, Murphy et al. (1996) reported synthesis from enterally delivered proline of relatively large amounts of citrulline and arginine and, to a much lesser extent, ornithine plus glutamate plus glutamine in piglets. These findings challenge the traditional concept that proline was not catabolized by intestinal mucosa (Wakabayashi 1995). Considering the relatively large mass of the small intestine compared with the liver and kidneys, the intestinal mucosa likely plays a major role in initiating proline degradation in the body (Wu 1997). Consistent with this suggestion is the recent finding that 38% of dietary proline was extracted in the first pass by PDV of milk protein-fed piglets, and thus substantial amounts of dietary proline were not available to extraintestinal tissues (Stoll et al. 1998b).

**Branched-chain amino acids (BCAA).** Both BCAA transaminase and branched-chain  $\alpha$ -ketoacid dehydrogenase are present in the intestinal mucosa (Harper et al. 1984), which provides an enzymatic basis for BCAA catabolism. About 30% of the total ingested dietary leucine is extracted by dog small intestine in the first pass, ~55 and ~45% of which enters transamination and protein synthesis, respectively (Yu et al. 1990). In adult humans, 20–30% of enterally delivered leucine is utilized in the first pass within the splanchnic bed (Biolo et al. 1992, Hoerr et al. 1993). In milk protein-fed piglets, 40% of leucine, 30% of isoleucine and 40% of valine in the diet are extracted by PDV in the first pass; <20% of the extracted BCAA are utilized for intestinal mucosal protein synthesis (Stoll et al. 1998b). In contrast, in sheep, the intestinal utilization of dietary leucine is directed mainly to protein synthesis, and there is limited catabolism of leucine by the small intestine (Cappelli et al. 1997). These results suggest substantial catabolism of dietary BCAA by the small intestinal mucosa in humans and monogastric animals, but not in ruminants. Although the metabolic fate of dietary BCAA in intestinal mucosa is not known, their nitrogen is likely used for alanine synthesis.

**Lysine, methionine, phenylalanine and threonine.** These amino acids were traditionally considered not to be catabolized by intestinal mucosa because of the reported absence or negligible activity of initial and other rate-controlling enzymes, including lysine: $\alpha$ -ketoglutarate reductase (Chu and Hegsted 1976), phenylalanine hydroxylase (Tourian et al. 1969), S-adenosyl-L-methionine synthase (Finkelstein 1990), threonine 3-dehydrogenase, threonine dehydratase and threonine aldolase (Le Floch et al. 1997). Because protease inhibitors were not used in preparing tissue extracts for assays of these enzymes and because protease activities are high in intestinal mucosa, the validity of the previously reported absence of amino acid-catabolizing enzymes from small intestine should be reexamined, as exemplified by our studies of intestinal proline oxidase (Wu 1997).

Stoll et al. (1998b) reported that ~50% of dietary lysine and methionine, 45% of dietary phenylalanine and 60% of dietary threonine were extracted in the first pass by PDV of milk protein-fed pigs. These authors estimated that <20% of the extracted essential amino acids was utilized for mucosal

protein synthesis, and one third of them were catabolized by small intestinal mucosa in the first pass. Similarly, in adult humans, 30 and 58% of enterally delivered lysine and phenylalanine are extracted in the first pass, respectively, within the splanchnic bed (Biolo et al. 1992, Hoerr et al. 1993). These results suggest that small intestinal mucosa may play an important role in degrading dietary essential amino acids; however, direct evidence for their catabolism is lacking.

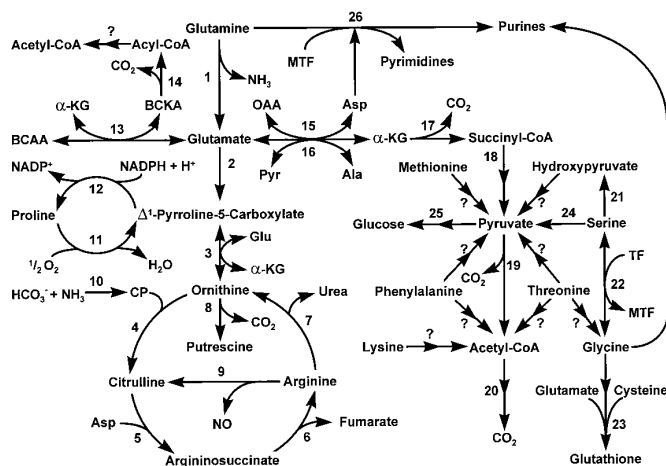
Methionine transamination occurs in small intestinal homogenates (Mitchell and Benevanga 1978), and glutamine transaminase K, whose major substrates include glutamine, phenylalanine and methionine, is widespread in mammalian tissues (Cooper and Meister 1977); however, their metabolic relevance remains unknown. In addition, there is evidence for phenylalanine transaminase activity in porcine aspartate transaminase isoenzymes (Shrawder and Martinez-Carrion 1972), abundant enzymes in intestinal mucosa (Windmueller 1982). Further enzymological work is required to establish biochemical bases for intestinal catabolism of essential amino acids.

### SIGNIFICANCE OF INTESTINAL AMINO ACID CATABOLISM

**Intestinal integrity and function.** Enteral feeding is the primary source of amino acids for intestinal mucosa because uptake of amino acids other than glutamine from arterial blood is low or insignificant (Windmueller 1982). Intestinal mucosal amino acid metabolism plays an important role in regulating intestinal integrity and function through the following mechanisms. First, as noted above, dietary glutamine, glutamate and aspartate, and arterial blood glutamine are major fuels for small intestinal mucosa and are responsible for providing energy required for intestinal ATP-dependent metabolic processes such as active nutrient transport and high rates of intracellular protein turnover (Burrin and Reeds 1997). Second, ornithine (a product of arginine, glutamine and proline) is the immediate precursor for polyamine synthesis, which is essential to proliferation, differentiation and repair of intestinal epithelial cells (Luk et al. 1980). Third, arginine is the physiologic precursor of NO, which plays an important role in regulating intestinal blood flow, integrity, secretion and epithelial cell migration (Alican and Kubes 1996). Fourth, glutamate, glycine and cysteine are precursors for the synthesis of glutathione, a tripeptide critical for defending the intestinal mucosa against toxic and peroxidative damage (Reeds et al. 1997). Our current knowledge of intestinal amino acid metabolism helps to explain why total parenteral nutrition selectively decreases protein synthesis in small intestinal mucosa and results in intestinal atrophy (Dudley et al. 1998) and further supports the notion that dietary amino acids are obligatory for maintaining intestinal mucosal mass and integrity.

**Endogenous synthesis of amino acids.** Proline is synthesized from dietary arginine, ornithine, glutamine, glutamate and aspartate, and from arterial glutamine in intestinal mucosa (Fig. 1). In vivo isotopic studies have demonstrated that small intestine is the major organ for synthesizing proline from dietary glutamate in pigs (Murphy et al. 1996) and humans (Matthews et al. 1993). The synthesis of proline from arginine is absent in enterocytes of suckling pigs and is markedly increased in cells from postweaning pigs due to induction of arginase (Wu et al. 1996). This provides a biochemical basis for explaining why proline is an essential amino acid for neonatal pigs, but not for postweaning pigs (Chung and Baker 1993).

An important aspect of intestinal amino acid catabolism is the synthesis of citrulline and arginine from glutamine and proline via P5C synthase and proline oxidase, respectively (Fig. 1). At birth, there are high rates of synthesis of citrulline and arginine in pig



**FIGURE 1** Intestinal mucosal amino acid catabolism. Enzymes that catalyze the indicated reactions are as follows: 1) phosphate-dependent glutaminase; 2)  $\Delta^1$ -pyrroline-5-carboxylate synthetase; 3) ornithine aminotransferase; 4) ornithine carbamoyltransferase; 5) argininosuccinate synthetase; 6) argininosuccinate lyase; 7) arginase; 8) ornithine decarboxylase; 9) nitric oxide synthase; 10) carbamoylphosphate synthetase; 11) proline oxidase; 12) pyrroline-5-carboxylate reductase; 13) BCAA transaminase; 14) BCKA dehydrogenase; 15) aspartate transaminase; 16) alanine transaminase; 17)  $\alpha$ -KG dehydrogenase; 18) possibly via NADP-linked malic enzyme, phosphoenolpyruvate carboxykinase/pyruvate kinase and oxaloacetate decarboxylase; 19) pyruvate dehydrogenase; 20) Krebs cycle enzymes; 21) serine transaminase; 22) serine hydroxymethyltransferase; 23) glutathione-synthesizing enzymes; 24) serine dehydratase; 25) glucose-synthesizing enzymes; and 26) purine- and pyrimidine-synthesizing enzymes. The symbol "?" denotes unknown reactions in intestinal mucosa. Abbreviations: Asp, aspartate; BCAA, branched-chain amino acids; BCKA, branched-chain  $\alpha$ -ketoacid dehydrogenase; CP, carbamoyl phosphate; Glu, glutamate;  $\alpha$ -KG,  $\alpha$ -ketoglutarate; MTF,  $N^5,N^{10}$ -methylene tetrahydrofolate; OAA, oxaloacetate; Pyr, pyruvate; TF, tetrahydrofolate.

enterocytes, which decrease progressively with postnatal growth (Wu 1997). In suckling young mammals, intestinal synthesis of citrulline provides  $\geq 50\%$  of daily arginine requirements (Wu and Knabe 1996), but this pathway alone is insufficient to meet the particularly high requirement of arginine for rapid growth (Visek 1984). In weaned animals, induction of intestinal P5C synthetase, which is mediated by glucocorticoids, results in increased synthesis of citrulline from glutamine (Flynn and Wu 1997). In healthy adults, the citrulline produced by the small intestine, which is converted into arginine mainly in kidneys, is sufficient to meet arginine requirements (Visek 1984). Because P5C synthetase is located almost exclusively in the intestinal mucosa, the small intestine plays an important role in endogenous synthesis of arginine in most mammals including humans, pigs and rats (Wakabayashi 1995).

Alanine is an important nitrogenous product of the intestinal catabolism of glutamine, glutamate, aspartate (Windmueller 1982) and perhaps BCAA. Thus, alanine transaminase appears to function primarily for alanine synthesis in intestinal mucosa. Alanine may serve to transport nitrogen of some dietary amino acids to extraintestinal tissues. Because liver actively takes up alanine and ammonia from portal and arterial blood and releases glutamine (Rémésy et al. 1997), and the small intestine substantially utilizes enteral and arterial blood glutamine and releases large amounts of alanine and ammonia during both the postabsorptive state and feeding (Windmueller 1982), there appears to be an extensive nitrogen recycling within the splanchnic bed. This splanchnic nitrogen recycling may be a mechanism for nitrogen sparing, particularly under food deprivation.

**Availability of dietary amino acids to extraintestinal tissues.** One theme that has emerged from this review is that

intestinal mucosal amino acid catabolism (Fig. 1) plays an important role in modulating the entry of absorbed dietary amino acids into portal circulation. Thus, the pattern of amino acids in the diet differs markedly from that in portal venous blood and does not reflect their availability to extraintestinal tissues (Stoll et al. 1998b). This concept has important implications for protein and amino acid nutrition. First, the extensive catabolism of dietary essential amino acids in the first pass by the small intestine, a large organ in the body, results in decreased nutritional efficiency. Because there is a positive correlation between first-pass intestinal catabolism of dietary amino acids and mucosal mass (Stoll et al. 1998b), factors that affect intestinal mass (e.g., growth hormone, insulin-like growth factor-I or diabetes) may have an important effect on requirements for dietary amino acids. Thus, intestinal amino acid catabolism should receive more attention from both animal and human nutritionists to maximize the utilization efficiency of dietary amino acids and optimize health. Second, because of developmental changes, disease-associated alterations and species differences in intestinal amino acid catabolism, these factors should be taken into consideration in recommending dietary amino acid requirements and in refining *in vivo* models of amino acid and protein metabolism (Stoll et al. 1998a).

## PROBLEMS AND AREAS FOR FUTURE RESEARCH

Recent intriguing findings of the extensive first-pass extraction of dietary amino acids by the human splanchnic bed (Battezzati et al. 1995, Castillo et al. 1993a, Hoerr et al. 1993) and by porcine PDV (Stoll et al. 1998b) raise an important question regarding their catabolism in small intestinal mucosa. This novel concept should be firmly established by biochemical studies with enterocytes. In addition, because arginine deficiency, which causes life-threatening hyperammonemia, occurs in preterm infants (Batshaw et al. 1984), and because aberrations of intestinal function remain a major factor for both morbidity and mortality in neonates (Odle et al. 1996), it is important to elucidate cellular and molecular mechanisms responsible for regulating intestinal amino acid catabolism and arginine synthesis during fetal and postnatal development. Finally, because dietary protein intake may play an important role in colon tumorigenesis (Visek 1986), amino acid metabolism in colonocytes, which is poorly understood (Burrin and Reeds 1997), should be quantified. Collectively, these studies will increase our understanding of intestinal amino acid catabolism and its role in nutrition and disease.

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