Amino Acids (2009) 37:105–110
DOI 10.1007/s00726-008-0152-4

REVIEW ARTICLE

Amino acids and gut function

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Received: 13 June 2008 / Accepted: 8 July 2008 / Published online: 1 August 2008

Abstract The intestine is not only critical for the absorption of nutrients, but also interacts with a complex external milieu. Most foreign antigens enter the body through the digestive tract. Dietary amino acids are major fuels for the small intestinal mucosa, as well as important substrates for syntheses of intestinal proteins, nitric oxide, polyamines, and other products with enormous biological importance. Recent studies support potential therapeutic roles for specific amino acids (including glutamine, glutamate, arginine, glycine, lysine, threonine, and sulfur-containing amino acids) in gut-related diseases. Results of these new lines of work indicate trophic and cytoprotective effects of amino acids on gut integrity, growth, and health in animals and humans.

Keywords Amino acids · Gut · Intestinal mucosa · Metabolism · Inflammation

Abbreviations

cNOS	Constitutive nitric oxide synthase
iNOS	Inducible nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
TPN	Total parenteral nutrition

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Introduction

The gut is an important organ responsible for digestion, absorption and metabolism of dietary nutrients. It contributes to 9–12% of whole-body protein synthesis (Reeds et al. 1997) and is the most important route of entry for foreign antigens, including food proteins, natural toxins, commensal gut flora, and invading pathogens (Li et al. 2007). The intact intestinal tract is lined by a continuous monolayer of intestinal epithelial cells, of which a primary function is to act as a physical barrier, interacting with a complex external milieu (Gewirtz et al. 2002). The intestinal tract is also one of the largest lymphoid organs in the body, and consists of immune cells in organized gut-associated lymphoid tissues (Field et al. 2002).

Amino acids are not only important substrates for the synthesis of proteins and other nitrogenous compounds, but also key regulators of fluxes through major metabolic pathways (Jobgen et al. 2006; Meijer 2003). Recent studies with animals and humans indicate additional roles for amino acids in maintaining gut health (Amin et al. 2002; Wang et al. 2008). The purpose of this article is to review current information regarding the critical role of amino acids in supporting gut barrier integrity and function.

Glutamine

L-Glutamine (Gln), an abundant amino acid in the body, has traditionally been considered as a nonessential amino acid but is now regarded as a conditionally essential nutrient under stress conditions, such as infection, injury, and weaning (Li et al. 2007; Wang et al. 2008). In addition to its role as an important fuel for both epithelial cells and leukocytes of the small intestine, Gln

participates in many key metabolic processes, such as protein synthesis, gluconeogenesis, inter-organ nitrogen transfer, nucleic acid biosynthesis, the immune response, and regulation of cellular redox state (Wu et al. 2007). Thus, dietary Gln supplementation decreases the susceptibility of enterocytes and lymphatic cells to apoptosis (Domeneghini et al. 2006), while enhancing anti-oxidative function and cell proliferation in the small intestine (Wang et al. 2008). The crucial importance of circulating or luminal Gln in supporting gut function and mucosal integrity was convincingly demonstrated by Baskerville et al. (1980), who reported that animals receiving intravenous infusion of glutaminase developed diarrhea, mild villous atrophy, mucosal ulcerations, and intestinal necrosis. Similarly, prolonged use of total parenteral nutrition (TPN) can lead to impairment of gut epithelial integrity and immune function (Thomas et al. 2005). Notably, supplementing Gln to TPN solution maintained the height of intestinal villi, the thickness of mucosa and the thickness of intestinal wall in endotoxemic rats (Qin et al. 1996). Additionally, dietary glutamine supplementation prevented jejunal atrophy in early-weaned piglets during the first week postweaning and improved growth performance during the next week (Wu et al. 1996). Furthermore, glutamine-enriched diet accelerates the transport of amino acids across the jejunal brush border (Frankel et al. 1993).

Glutamate

L-Glutamate (Glu) is produced from Gln by glutaminase in the small intestine (Wu 1998). Dietary glutamate is almost completely metabolized by the gut of neonatal pigs during absorption (Reeds et al. 1996). Furthermore, dietary Glu is a specific precursor for the intestinal synthesis of glutathione, arginine and proline (Reeds et al. 1997; Wu and Morris 1998). Thus, enteral Glu is of critical importance in intestinal metabolism and physiology. At present, studies on the roles of Glu supplementation in the treatment of gut diseases are limited. Using a burn injury model of rats, Hasebe et al. (1999) reported that Glu could be a preferable fuel to Gln for enterocytes when glutaminase activity was low. However, it remains unknown whether Glu can effectively substitute Gln in the diet under any conditions. Nonetheless, in endotoxemic rats, a Glu-enriched diet can counteract glutamine depletion and Glu displays a trophic effect restricted to the jejunum (Chambon-Savanovitch et al. 1999). Further, AminoGut, which contains both glutamine and glutamate, has been recently developed to enhance intestinal function and growth performance in pigs (Wu et al. 2007).

Arginine

L-Arginine (Arg) is an essential substrate for the synthesis of important molecules, including nitric oxide (NO), polyamines, and creatine (Wu and Morris 1998). In addition, there is emerging evidence that Arg activates the mTOR signaling pathway in the small intestine (Corl et al. 2008). Therefore, Arg has many fundamental roles in cell metabolism and physiology. In postweaning mammals, the small intestine is a major site for Arg metabolism (Wu 1998). Of particular interest, enterocytes of most mammals (including pigs, rats, and humans) are responsible for the endogenous synthesis of Arg, which plays a critical role in maintaining Arg homeostasis in neonates (Wu et al. 2004b). A large number of animal and human studies have identified an important role for Arg in intestinal immune response (Li et al. 2007).

Over the past decade, much attention has been directed to study the role of NO in mediating the beneficial effect of arginine in intestinal function. Arg stimulates intestinal fluid secretion through a NO mediated mechanism (Alican and Kubes 1996). Conversely, an inhibition of NO synthase (NOS) leads to decreased intestinal secretion, resulting in intestinal ischemia (Kanwar et al. 1994). The inducible isoform of NOS (iNOS) produces a quantitatively larger amount of NO, whereas the constitutive form of NOS (cNOS), which includes endothelial NOS (eNOS) and neuronal NOS (nNOS), generates relatively a small amount of NO in the small intestine (Alican and Kubes 1996). NO produced by cNOS is of critical importance in the maintenance of intestinal mucosal barrier (Kanwar et al. 1994).

Although the role of iNOS in mediating intestinal inflammation was previously controversial, the results from many experimental models of colitis in iNOS-deficient mice suggest that iNOS also plays an important role in mucosal inflammation. For example, overexpression of iNOS in leukocytes decreased granulocyte mucosal infiltration in the early phases of damage (McCafferty et al. 1999). Conversely, iNOS-deficiency resulted in greater macroscopic mucosal damage (McCafferty et al. 1997). Additionally, Arg maximally stimulates intestinal cell migration depending on both NO production (Rhoads et al. 2004) and p70S6 kinase signaling (Rhoads et al. 2008). It should be recognized that excess production of NO by iNOS is detrimental to intestinal cells.

Arg supplementation is effective in improving intestinal barrier function and vascular development. For example, oral Arg decreases the mucosal injury caused by lipopolysaccharide endotoxemia in animals (Sukhotnik et al. 2004), as indicated by ameliorated mucosal morphology and increased cell proliferation. Furthermore, pretreatment with Arg enhances survival and intestinal mucosal barrier function after intestinal mesenteric ischemia (Schleiffer

and Raul 1996). Additionally, studies with rat models of intestinal transplantation have demonstrated that pretreatment with Arg prevents the disruption of the basement membrane (Mueller et al. 1998) and improves the morphology of small bowel (Mueller et al. 2000). Moreover, Arg-enriched diets protect gut mucosa from injury induced by radiation-induced enteritis, as indicated by accelerated healing ability, as well as prevention of bacterial translocation and weight loss (Ersin et al. 2000; Gurbuz et al. 1998). The effect of Arg may be dose-dependent, because a recent study revealed that dietary supplementation with lower level of Arg (0.7%) had beneficial effect on microvascular development of early-weaned pigs, but a higher level of Arg supplementation (1.2%) causes adverse effects, including aggravation of weaning stress and gut dysfunction (Zhan et al. 2008). This further supports the view that a proper balance between Arg and other amino acids in the diet is crucial for beneficial effects of Arg on whole-body homeostasis (Wu et al. 2007).

Sulfur containing amino acids and their metabolites

Sulfur containing amino acids and their metabolic products are of importance in growth and health. L-Methionine (Met) is a nutritionally essential amino acid. However, L-Cysteine (Cys) is classified as a semiessential amino acid for neonates because of a low ability to convert Met to Cys through transmethylation and transsulfuration (Finkelstein 2000). The major end products of Met and Cys metabolism are glutathione (GSH), homocysteine (Hcy) and taurine (Tau), which play important roles in the intestinal immune response (Grimble 2006). Interestingly, 2-hydroxy-4-methylthiobutyrate (a Met metabolite) has recently been reported to regulate eNOS expression, blow flow, and absorption of amino acids by the pig small intestine (Fang et al. 2008).

A number of studies suggest the presence of first-pass splanchnic metabolism for dietary methionine, predominantly in intestinal tissue (Shoveller et al. 2003). Net intestinal utilization of Met is substantial and may account for up to 52% of the dietary intake (Wu 1998). Notably, recent findings indicate that Met degradation is negligible in pig enterocytes and suggest that intestinal luminal microbes are responsible for the extensive catabolism of dietary Met by the gut (Chen et al. 2007). In addition, extensive intestinal utilization of Cys has been suggested, as the appearance of dietary Cys in the portal blood is very limited (less than 20% of dietary intake) (Stoll et al. 1998). However, what cell types are responsible for Cys catabolism in the small intestine remains unknown.

GSH, which consists of glycine, Glu and Cys, is the major intracellular low-molecular-weight thiol and plays important roles in antioxidant defense, nutrient metabolism and cytoprotective events (Wu et al. 2004a). GSH in the gut lumen and enterocytes is of critical importance in maintaining normal intestinal function, in part, by protecting epithelial cells from damage by electrophiles and fatty acid hydroperoxides (Aw et al. 1992). Intracelluar GSH concentrations are higher in actively proliferating cells and decrease gradually as cells become quiescent (Shaw and Chou 1986). Increased oxidation of the GSH/glutathione disulfide redox was observed in Caco-2 cells during differentiation (Nkabyo et al. 2002). A more reduced GSH redox potential was related to increased cell density, but a more oxidized potential was associated with decreased cell density (Hutter et al. 1997). Thus, GSH appears to be involved in the regulation of cell growth. Consequently, a deficiency of GSH, due to an inhibition of its synthesis by buthionine sulfoximine, leads to severe mucosal damage, marked by epithelial cell damage, mitochondrial degeneration and villus atrophy in mice (Martensson et al. 1989). Importantly, oral administration of GSH or GSH monoester can prevent such damage (Martensson et al. 1989). Furthermore, the GSH redox cycle is considered to be a key intracellular antioxidant mechanism to promote intestinal hydroperoxide removal and reduce lymphatic peroxide transport in vivo (Aw and Williams 1992) and in vitro (Wingler et al. 2000). Thus, administration of specific dietary substrates and precursors for GSH synthesis is an effective strategy to improve gut mucosal functions and may prevent or treat intestinal diseases (Wu et al. 2004a).

Taurine is an end-product of sulfur containing amino acid metabolism and involved in many physiological processes such as osmoregulation, anti-oxidative responses, detoxification, membrane stabilization, as well as retinal and cardiac function (Huxtable 1992). Taurine constitutes more than 50% of the free amino acid pool of lymphocytes, which may indicate its importance in immune and proinflammatory responses (Redmond et al. 1998). In addition, taurine is present in duodenal mucosa at 90–100 times the concentration found in human plasma, indicating an accumulation of taurine in intestinal epithelium (Ahlman et al. 1993). Available evidence shows that taurine can prevent the effects of cellular lipid peroxidation on paracellular permeability in human intestinal Caco-2 cells (Roig-Pérez et al. 2004).

Glycine and lysine

Glycine and lysine have been recently postulated to have protective effects on the gut. Utilization of glycine by the small intestinal mucosa to synthesize GSH is a physiologically important pathway (Reeds et al. 1997), but the role of glycine as a powerful cytoprotectant has only

recently been recognized. The mechanisms of action include osmoprotection, extracellular signaling, scavenging of oxygen free radicals, and modification of biologically active molecules (Hall 1998). One study suggested that local perfusion with glycine diminishes ischemia-reperfusion injury in the small intestinal mucosa, as indicated by increased mucosal protein content, increased mucosal DNA content, and maintenance of mucosal glutaminase activity, during either the pre-ischemia phase or the pre-reperfusion phase in a rat model (Lee et al. 2002). This finding is important because the loss of gut barrier function frequently occurs in patients with ischemia-reperfusion injury (Alican and Kubes 1996).

Studies with animals show that dietary glycine and lysine are directly utilized by the intestine for protein synthesis and other metabolic processes (Stoll et al. 1998). Van Goudoever et al. (2000) demonstrated that the intestinal oxidation of lysine in piglets receiving a high protein diet accounts for 30% of the total lysine oxidation. They speculated that metabolism of the amino acids is needed to maintain the integrity and function of the gut, as well as to synthesize intestinal mucins and immunoglobulins. It is now clear that pig enterocytes do not degrade lysine (Chen et al. 2007). Thus, intestinal luminal bacteria are likely responsible for the extensive catabolism of dietary lysine. At present, little is known about a role of lysine in gut function. However, Gu (2000) reported that dietary lysine supplementation increased glycogen content and villous height in distal jejunum and ileum of pigs.

Threonine

Among the essential amino acids, threonine is particularly important for mucin synthesis and maintenance of gut barrier integrity (Bertolo et al. 1998). The retention of dietary threonine by the intestine (up to 60%) is high (Stoll et al. 1998). In intestinal mucosa, a major fate of threonine is incorporation into mucins, which are major glycoproteins protecting the epithelium from injury (Le Floc'h and Sève 2005; Schaart et al. 2005). A study with rats demonstrated that dietary threonine restriction dramatically and specifically impaired the synthesis of mucins in all segments of the small intestine, reaching the largest reduction of 40% in the duodenum (Faure et al. 2005). In addition, Wang et al. (2007) reported that both a deficiency and an excess of dietary threonine reduced the synthesis of intestinal mucosal protein and mucins in young pigs. The implications of threonine for intestinal health and nutritional requirements have been highlighted in several recent studies. For example, the threonine utilization for syntheses of small intestinal proteins is increased substantially in response to sepsis, representing over two-fold of the threonine intake (Faure et al. 2007). Thus, under inflammatory conditions, threonine availability may become limited for the synthesis of intestinal mucins, which leads to an impairment of gut barrier function. Consequently, an increase in dietary provision of threonine and other amino acids can promote mucin synthesis and reequilibrate the gut microbiota to favor intestinal protection and mucosal healing (Faure et al. 2006).

Concluding remarks and perspective

The gut plays a key role in barrier defense in addition to digestion, absorption and metabolism of nutrients. Thus, it is important to develop new trophic methods to maintain or improve gut integrity and function under stress conditions. Findings from studies with both animals and humans indicate an increasingly recognized and critical role for dietary amino acids in maintaining gut health and preventing intestinal diseases. At present, little is known about a role for branched-chain amino acids in intestinal barrier integrity, which will likely become an important topic of intensive investigation in the future. Based on current knowledge, glutamine, glutamate, arginine, glycine, lysine, threonine, and sulfur-containing amino acids are expected to hold great promise in the management of a wide array of gut-related disorders in both humans and animals.

Acknowledgments The authors are grateful to the National Natural Science Foundation of China for supporting our research.

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