Amino Acids (2013) 45:443–450
DOI 10.1007/s00726-012-1325-8

INVITED REVIEW

Regulation of intestinal protein metabolism by amino acids

Julien Bertrand · Alexis Goichon · Pierre Déchelotte · Moïse Coëffier

Received: 1 March 2012 / Accepted: 15 May 2012 / Published online: 29 May 2012

Abstract Gut homeostasis plays a major role in health and may be regulated by quantitative and qualitative food intake. In the intestinal mucosa, an intense renewal of proteins occurs, at approximately 50 % per day in humans. In some pathophysiological conditions, protein turnover is altered and may contribute to intestinal or systemic diseases. Amino acids are key effectors of gut protein turnover, both as constituents of proteins and as regulatory molecules limiting intestinal injury and maintaining intestinal functions. Many studies have focused on two amino acids: glutamine, known as the preferential substrate of rapidly dividing cells, and arginine, another conditionally essential amino acid. The effects of glutamine and arginine on protein synthesis appear to be model and condition dependent, as are the involved signaling pathways. The regulation of gut protein degradation by amino acids has been minimally documented until now. This review will examine recent data, helping to better understand how amino acids regulate intestinal protein metabolism, and will explore perspectives for future studies.

Keywords Amino acids · Arginine · Glutamine · Intestine · Protein metabolism · Signaling pathways

J. Bertrand · A. Goichon · P. Déchelotte · M. Coëffier (✉)
INSERM UMR 1073, 22 bd Gambetta,
76183 Rouen cedex, France
e-mail: moise.coeffier@univ-rouen.fr

J. Bertrand · A. Goichon · P. Déchelotte · M. Coëffier
Institute for Research and Innovation in Biomedicine,
University of Rouen, Rouen, France

P. Déchelotte · M. Coëffier
Nutrition Unit, Rouen University Hospital, Rouen, France

Abbreviations

FSR	Fractional synthesis rate
GCN2	General controller non-derepressible 2 kinase
MAPK	Mitogen activated protein kinase
mTOR	Mammalian target of rapamycin
NO	Nitric oxide

Introduction

Maintenance of intestinal protein metabolism plays a key role in gut homeostasis and the regulation of gut barrier function, which is essential in the defence of the organism. Many stress events, chronic inflammatory diseases and infections have been associated with an increased intestinal permeability and consequently a dysregulation of gut homeostasis (Turner 2009). Gut protein metabolism has to be tightly regulated since protein fractional synthesis rate (FSR) approaches approximately 50 % per day in human duodenal mucosa (Nakshabendi et al. 1996; Coeffier et al. 2003a), a value higher than that of other major tissues, such as the liver or the muscle. However, this value is dependent of the precursor pool and the tracer used. For instance, in fasting conditions, FSR ranged between 28.0 and 88.2 %/d using intracellular free amino acids and plasma amino acids as precursor pool, respectively, for $^{2}H_{5}$-phenylalanine, while it ranged between 23.0 and 40.0 %/d for ^{13}C-leucine (Bouteloup et al. 1998). In addition, intestinal protein FSR also varies among models and can reach approximately 50–60 %/d in piglets (Murgas Torrazza et al. 2010; Yin et al. 2010) and 100 %/d in rats (Boukhettala et al. 2009; El Yousfi et al. 2003). Previous studies reported that nutritional status can affect gut protein synthesis (Bouteloup et al. 1998; Winter et al. 2007). Amino

acids, as constituents of proteins and signaling molecules, modulate intestinal protein metabolism, particularly protein synthesis, and some amino acids such as glutamine, arginine and leucine exert distinct effects. Proteolytic pathways are involved in the regulation of several major cellular processes, i.e., cell proliferation, apoptosis, and inflammatory and stress responses. Although these pathways have been described in the intestine of different species, the investigation of regulatory effects of amino acids on protein degradation has just been initiated. This article will review recent advances on the effects of nutritional status and specific amino acids on intestinal protein metabolism regulation and will discuss the involved signaling pathways.

Influence of fasting, feeding and nutritional status on intestinal protein metabolism

Because the gut takes up its substrates mainly from the luminal side, providing both energy and precursors for protein synthesis, it may be anticipated that protein synthesis and degradation would be altered over the fast-feeding cycle, and also according to nutritional stores, as in the case of prolonged starvation or when nutrients are supplied intravenously.

In rats, short-term food restriction does not influence jejunal mucosal protein synthesis (Boukhettala et al. 2009) but it does increase lysosomal-mediated protein degradation (Boukhettala et al. 2009; Samuels et al. 1996). In vitro data suggest that prolonged nutritional deprivation decreases protein synthesis in intestinal epithelial cells through activation of GCN2 pathway (Boukhettala et al. 2012; Le Bacquer et al. 2003). On the other hand, an early study in healthy volunteers found similar duodenal FSR in fed and fasted conditions (Bouteloup et al. 1998); however, in the so-called "fed" state, food intake had been stopped several hours before the endoscopic biopsies were taken, on the basis of safety issues due to endoscopy procedure. Indeed, we recently showed that a 5-h enteral infusion of a mixed oral nutritional supplement, containing carbohydrates and proteins, markedly (twofold) increased duodenal protein synthesis as compared with fasting (Coeffier et al. 2008). Although intestinal villus atrophy has been reported during prolonged malnutrition in animals (Belmonte et al. 2007; Tandon et al. 1968), FSR in the gastric or duodenal mucosa of malnourished patients was not altered (Winter et al. 2007). Similar results have been observed in the jejunal mucosa of malnourished rats (Tannus et al. 2009). In contrast, refeeding restored intestinal trophicity (Tandon et al. 1968) and increased FSR both in gastric and duodenal mucosa (Winter et al. 2007). Altogether, these data suggest that villus atrophy could occur during starvation without a reduction in protein synthesis, and may be due mainly to increased proteolysis, while refeeding restores intestinal trophicity through increased protein synthesis, and may be some inhibition of proteolysis. This hypothesis, however, remains speculative since studies combining the study of protein synthesis and degradation in models of fasting feeding or prolonged starvation are still awaited.

Regarding specific nutrients, luminal amino acids reduce mucosal protein synthesis using perfused isolated jejunal segments in piglets (Adegoke et al. 1999), but we recently provided evidence that intragastric provision of proteins markedly stimulates duodenal protein synthesis in healthy volunteers (Coëffier et al. 2011). In contrast, intravenous amino acid infusion decreases colonic mucosal protein synthesis in postoperative patients (Rittler et al. 2005). The effects of some specific amino acids, i.e., glutamine, arginine and leucine (Table 1), are discussed below.

Glutamine and intestinal protein metabolism

Glutamine is the most abundant amino acid in plasma and is involved in a wide variety of metabolic and biochemical processes. Glutamine contributes to the regulation of the redox status as a precursor of glutathione (Belmonte et al. 2007) and also contributes to the synthesis of purine and pyrimidine bases, and, consequently, of nucleic acids (Labow and Souba 2000). Although initially classified as a non-essential amino acid since it can be synthesised de novo, glutamine has been more recently considered as conditionally essential in catabolic states wherein endogenous production and food intake cannot match the increased demand in different tissues (Labow and Souba 2000). In critically ill patients, plasma glutamine concentration is reduced (Dechelotte et al. 2006; Houdijk et al. 1998), and low glutamine is predictive of poor clinical outcome (Planas et al. 1993). In contrast, glutamine supplementation has been associated with a better clinical outcome in some studies, which could be related, among other mechanisms, to the preservation of gut barrier function (De-Souza and Greene 2005).

Glutamine is also the preferential substrate of rapidly dividing cells such as enterocytes and immune cells, and thus stimulates their proliferation (Calder and Yaqoob 1999; Rhoads et al. 1997). In intestinal diseases, e.g. Crohn's disease (Sido et al. 2006) or irritable bowel syndrome (Zhou et al. 2010), the expression of glutamine synthase is decreased in the small bowel and colonic mucosa, thus reducing the ability of intestinal cells to produce endogenous glutamine from other precursor amino acids. Accordingly, glutamine content is also reduced in the inflamed mucosa of Crohn's disease patients (Sido et al.

2006), which could contribute to energy deficit and immunological imbalance. Glutamine supplementation also improved gut barrier function in several experimental conditions of injury (Amasheh et al. 2009) and in some clinical situations (De-Souza and Greene 2005; van der Hulst et al. 1993). These beneficial effects are likely to be related to the modulation of intestinal protein metabolism by glutamine in favour of a positive nitrogen economy in the gut.

As a matter of fact, in vitro studies suggest that glutamine deprivation and supplementation influence intestinal protein metabolism. Indeed, in monolayers of Caco-2 cells, glutamine deprivation decreased protein FSR and electrical resistance (Le Bacquer et al. 2001), suggesting that maintenance of protein synthesis was mandatory to secure the efficiency of the tight-junction system. Recently, we provided evidence that glutamine deprivation decreased protein synthesis in HCT-8 cells through the stimulation of the GCN2 pathway, despite an activation of mTOR pathways (Boukhettala et al. 2012). Other authors have shown that mTOR and p38 MAPK activation induced by glutamine deprivation inhibited autophagic processes (Sakiyama et al. 2009), which contribute to cell survival during physiological stress. However, the stimulation of mTOR pathway by glutamine deprivation has not been found by others (Xi et al. 2012).

In contrast to glutamine deprivation, glutamine supplementation increased protein synthesis in Caco-2 (Le Bacquer et al. 2003), HCT-8 (Boukhettala et al. 2012) and IPEC-1 cells (Xi et al. 2012). Glutamine also increased protein synthesis in isolated enterocytes from either control (Higashiguchi et al. 1993) or septic rats (Higashiguchi et al. 1995). Interestingly, two recent studies showed that glutamine supplementation increased phosphorylation of 4EBP-1 and p70S6kinase, two downstream proteins in the mTOR pathway (Boukhettala et al. 2012; Xi et al. 2012), while glutamine supplementation had failed to stimulate mTOR pathway in a previous study (Nakajo et al. 2005). Different doses of glutamine used in these studies could explain this discrepancy. Protein degradation was limited by glutamine supplementation in porcine intestinal epithelial cells (Xi et al. 2012), while proteasome activity is not affected in human Caco-2 cells (Hubert-Buron et al. 2006).

Animal studies have revealed contradictory results. Indeed, using perfused jejunal segments, Adegoke et al. (1999) showed that glutamine decreased FSR. In malnourished rats, glutamine did not affect intestinal protein synthesis (Tannus et al. 2009) while glutamine increases duodenal protein synthesis in hypercatabolic dogs (Humbert et al. 2002). A diet containing glutamine is also able to maintain jejunal FSR during mucositis in rats (Boukhettala et al. 2010). Interestingly, two studies have evaluated the effects of intravenous glutamine supplementation. Intestinal protein synthesis was not affected by glutamine infusion both in healthy dogs (Marchini et al. 1999) and in septic rats (Holecek et al. 2006).

In healthy humans, we reported that enteral glutamine stimulates duodenal protein synthesis compared with saline, an effect that could be obtained also with an isonitrogenous mixture of non-essential amino acids (Coeffier et al. 2003a). However glutamine, but not control amino acids, decreased ubiquitin mRNA level in this study (Coeffier et al. 2003a), as it was also reported in piglets (Adegoke et al. 2003). An oral nutritional supplement containing glutamine markedly stimulated duodenal protein synthesis in healthy humans but this effect was not mainly related to glutamine (Coeffier et al. 2008). In hypercatabolic subjects (Bouteloup et al. 2000), glutamine stimulated duodenal protein synthesis, but the difference only approached statistical significance in this study of a small number of subjects ($n = 6$). In summary, in humans, as in animals, and in contrast to intestinal cells, glutamine by itself does not have trophic effect, at least in healthy conditions.

When moving on to metabolic processes and specific proteins, it appears that glutamine is able to regulate several metabolic pathways. During control, apoptotic, or inflammatory conditions induced in Caco-2 cells, we found using proteomics that 41, 45, and 8 % of the glutamine-affected proteins were involved in protein synthesis or degradation (Thebault et al. 2006; Deniel et al. 2007). Other proteins modulated by glutamine are involved in the regulation of gut barrier function, in inflammatory or stress responses. For example, glutamine deprivation is associated with a reduction of tight-junction protein expression (Li et al. 2004) and an increase of pro-inflammatory cytokines (Liboni et al. 2005). In contrast, glutamine supplementation preserves tight-junction proteins (Vermeulen et al. 2011; Li et al. 2004) and limits the production of pro-inflammatory cytokines (Aosasa et al. 2003; Coeffier et al. 2001, 2002, 2003b; Hubert-Buron et al. 2006; Marion et al. 2004). Interestingly, these effects may be mediated by the regulation of the ubiquitin–proteasome system. Indeed, glutamine is able to regulate ubiquitination process. For instance, glutamine limits IκBα ubiquitination, its degradation and the related inflammatory response without affecting proteasome activity (Hubert-Buron et al. 2006). In another tissue, i.e. lung, the limitation of IκBα ubiquitination by glutamine is mediated by the regulation of specific E3-ubiquitin ligase (Singleton and Wischmeyer 2008).

Thus, although in vitro data suggest that glutamine is able to regulate protein synthesis, in vivo data obtained both in animals and in humans remain controversial. Further studies evaluating the effects of glutamine supplementation on intestinal protein metabolism should be performed in specific pathophysiological conditions and should include mechanisms of action.

Table 1 Effects of individual amino acids on intestinal protein synthesis and involved signaling pathways

Models		Protein synthesis	Signaling pathways	References
Glutamine				
In vitro, Caco-2 cells (human)	Deprivation	Decreased	–	Le Bacquer et al. (2001)
In vitro, HCT-8 cells (human)	Deprivation	Decreased	↑ GCN2, ↑ mTOR	Boukhettala et al. (2012)
	Supplementation	Increased	↑ mTOR	
In vitro, IPEC-1 cells (porcine)	Deprivation	Decreased	↓ mTOR	Xi et al. (2012)
	Supplementation	Increased	↑ mTOR	
In vitro, Caco-2 cells (human)	Supplementation	Increased	–	Le Bacquer et al. (2003)
In vitro, Caco-2 cells (human)	Deprivation	–	↑ mTOR	Sakiyama et al. (2009)
In vitro, isolated enterocytes (rat)	Supplementation	Increased	–	Higashiguchi et al. (1993)
Jejunal segment (piglets)	Supplementation	Decreased	–	Adegoke et al. (2003)
In vivo, healthy humans	Supplementation	Increased	–	Coeffier et al. (2003a)
In vivo, malnourished rats	Supplementation	Unaffected	–	Tannus et al. (2009)
In vivo, hypercatabolic dogs	Supplementation	Increased	–	Humbert et al. (2002)
Arginine				
In vitro, IPEC-J2 cells (porcine)	Supplementation	Increased	↑ mTOR, NO independent	Bauchart-Thevret et al. (2010)
In vitro, IPEC-1 cells (porcine)	Supplementation	Increased	↑ mTOR	Tan et al. (2010)
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR, NO dependent	Ban et al. (2004)
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR	Nakajo et al. (2005)
In vitro, IEC6 cells (rat)	Supplementation	–	↑ mTOR	Rhoads et al. (2006)
In vitro, cdx2 cells (rat)	Supplementation	–	↑ mTOR, NO dependent	Rhoads et al. (2008)
In vivo, healthy humans	Supplementation	Unaffected	–	Claeyssens et al. (2007)
In vivo, rat (enteritis)	Supplementation	Increased	↑ mTOR	Corl et al. (2008)
Leucine				
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR	Ban et al. (2004)
In vitro, IEC16, 18 cells (rat)	Supplementation	–	↑ mTOR	Nakajo et al. (2005)
In vitro, cdx2 cells (rat)	Supplementation		↑ mTOR	Rhoads et al. (2008)
In vivo, neonatal pigs	Supplementation	Increased	↑ mTOR	Murgas Torrazza et al. (2010)
In vivo, weaning pigs	Supplementation	Increased	–	Yin et al. (2010)
In vivo, healthy humans	Supplementation	Unaffected	–	Coeffier et al. (2011)

FSR fractional synthesis rate, *GCN2* general controller non-derepressible 2 kinase, *mTOR* mammalian target of rapamycin, *NO* nitric oxide

Arginine and intestinal protein metabolism

Arginine is considered as a conditionally essential amino acid, because its needs are increased during metabolic stress (Nieves and Langkamp-Henken 2002) as well as during organ maturation and development (Wu et al. 2009). The immunological effects of arginine supply have been extensively described, mainly through the nitric oxide (NO) pathway. However, arginine may also support other vital functions, such as neonatal development and healing (Wu et al. 2009). Arginine may act by several mechanisms. Indeed, arginine is a precursor of proline, which plays a key role in collagen synthesis (Barbul et al. 1990). Arginine supply enables the synthesis of polyamines, which are implicated in mucosal repair (Moinard et al. 2005). Arginine may also be a potent secretagogue and may promote the release of endocrine and neuroendocrine hormones, such as growth hormone, insulin-like growth factor-1 (IGF-1), insulin, glucagon, and pancreatic polypeptide (Wu et al. 2009). Beneficial effects of arginine supplementation could be partly mediated by a modulation of protein turnover since arginine is a major carrier of nitrogen in humans and animals with four nitrogen atoms per molecule.

In vitro data underlined the ability of arginine to increase phosphorylation of S6K and 4EBP-1 in rat intestinal epithelial cells (Nakajo et al. 2005; Ban et al. 2004). These effects are blocked by NOS inhibitors (Ban et al. 2004). Activation of the mTOR pathway by arginine occurs during enterocyte migration, along with a requirement for NO production (Rhoads et al. 2006, 2008; Rhoads and Wu 2009). In neonatal porcine intestinal epithelial IPEC-J2 cells, arginine also stimulates protein synthesis through activation of mTOR pathway, but independently of NO production (Bauchart-Thevret et al. 2010). In LPS-treated IPEC-1 cells, arginine supplementation is able to increase protein synthesis (Tan et al. 2010). In addition, using

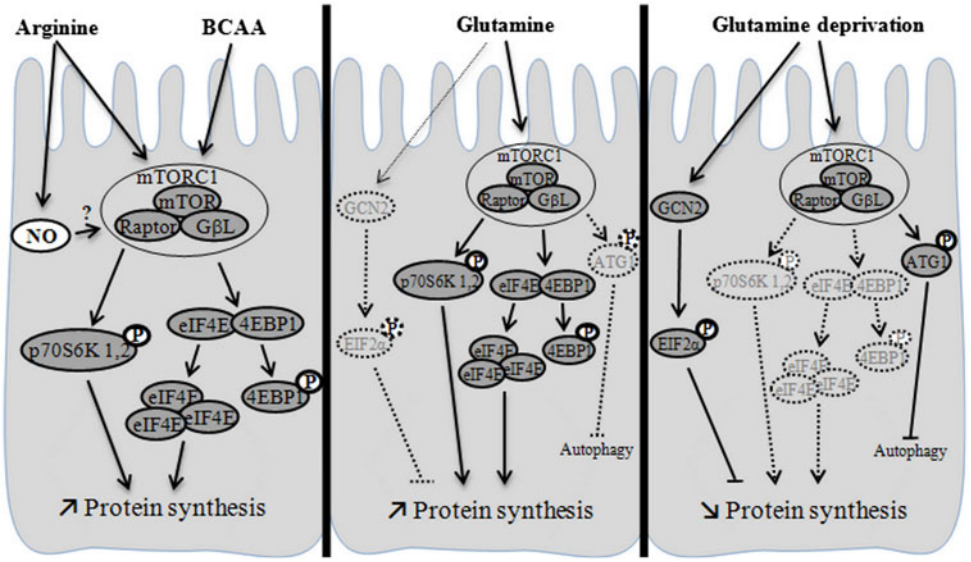

Fig. 1 Potential signalling pathways involved in the regulation of protein synthesis by amino acids. *Black and dashed lines* are representative of activated and inactivated pathways, respectively

proteomics in Caco-2 cells, Lenaerts et al. (2007) reported that arginine modulates the expression of proteins involved in proliferation, apoptosis and in heat shock response. All these in vitro data suggest that arginine stimulates protein synthesis in intestinal cells, although intracellular mechanisms could differ within cell types.

Animal studies have provided contrasting data on the modulation of whole-body (Bruins et al. 2002) and liver, muscle and kidney protein metabolism (Cui et al. 1999; Leon et al. 1991) in animals fed with arginine-enriched diets. During rotavirus-induced enteritis, arginine supplementation increased protein synthesis in intestinal mucosa (Corl et al. 2008). In this latter study, mTOR pathway was activated in arginine-fed animals, and the effects of arginine were blunted by rapamycin, an inhibitor of this pathway (Corl et al. 2008). In addition, the increased protein synthesis induced by arginine was associated with a reduction of intestinal permeability (Corl et al. 2008).

In humans, we previously reported that enteral supply of arginine did not affect FSR of duodenal protein in fasting healthy humans (Claeyssens et al. 2007). However, we cannot exclude that arginine may regulate intestinal protein metabolism in other conditions including injury. Surprisingly, to our knowledge, the effects of arginine on protein degradation have not yet been documented.

Branched chain amino acids and gut protein metabolism

The effects of branched chain amino acids on protein metabolism have been well established in muscle (Wu 2009) but have been little documented in the intestine until recently. In vitro data have suggested that leucine is able to activate mTOR pathway in intestinal epithelial cells as in muscle cells (Ban et al. 2004; Nakajo et al. 2005; Rhoads et al. 2008). In addition, leucine supplementation increased cell migration (Rhoads et al. 2008). The supplementation of low-protein diets with leucine was associated with an increase of protein synthesis and an activation of mTOR pathway in the jejunal mucosa of neonatal pigs (Murgas Torrazza et al. 2010). A similar effect was observed in proximal and distal small intestine but not in the colon of weaning pigs fed with 1.61 % of leucine in the diet (Yin et al. 2010). Interestingly, stimulation of protein synthesis is maintained, while increasing leucine provision to 1.88 % of diet in the distal small intestine but not in the proximal small intestine (Yin et al. 2010). In healthy humans, we recently reported that a high dose leucine supplementation did not affect duodenal protein synthesis (Coeffier et al. 2011). This result could be explained by the decrease of isoleucine and valine plasma concentration after leucine supplementation observed in humans, which might become a rate limiting factor for synthesis (Coeffier et al. 2011). Reduced threonine plasma concentrations may also occur in response to leucine supplementation in weaning pigs (Yin et al. 2010). To our knowledge, only one study from our group evaluated so far the effects of leucine supplementation on intestinal protein degradation and showed that leucine reduced proteasome activity in the duodenal mucosa (Coeffier et al. 2011). No data are available yet in pathophysiological conditions, but further evaluation of the impact of leucine on gut protein metabolism during inflammation or septic states looks warranted.

Conclusions and perspectives

In conclusion, although the effects of amino acids on intestinal protein metabolism are model and condition

dependent, available data show that glutamine and arginine may be able to modulate intestinal protein synthesis. The effects of arginine seem to be more pronounced in severely injured conditions associated with either arginine depletion or intestinal damage. For glutamine, similar observations may apply. However, further studies are needed to confirm this point. Concerning the signaling pathways involved in the regulation of protein synthesis by amino acids, it is well established that arginine effects are mediated by mTOR pathway; the role of NO remains controversial (Fig. 1). The signalling pathways involved in glutamine effects have to be clarified, but we speculate that glutamine supplementation is able to activate downstream components of mTOR and then protein synthesis, while glutamine depletion activates GCN2 pathway leading to a limitation of protein translation (Fig. 1). The effects of amino acids on protein degradation remain poorly documented. Further studies are needed (i) to investigate the influence of amino acids on intestinal protein degradation, and thus attain global insight into intestinal protein metabolism and (ii) to evaluate the effects of glutamine and arginine combination. Indeed, combined glutamine and arginine have been recently associated with interesting effects on gut inflammatory and antioxidant responses (Coeffier and Dechelotte 2010; Gennari et al. 1995; Kul et al. 2009; Lechowski et al. 2012; Lecleire et al. 2008), but intestinal protein metabolism has not been studied.

Acknowledgments This work was supported by the French Agency for Research (Agence Nationale pour la Recherche, ANR-07-PNRA-020).

References

Adegoke OA, McBurney MI, Samuels SE, Baracos VE (1999) Luminal amino acids acutely decrease intestinal mucosal protein synthesis and protease mRNA in piglets. J Nutr 129(10):1871–1878

Adegoke OA, McBurney MI, Samuels SE, Baracos VE (2003) Modulation of intestinal protein synthesis and protease mRNA by luminal and systemic nutrients. Am J Physiol Gastrointest Liver Physiol 284(6):G1017–G1026

Amasheh M, Andres S, Amasheh S, Fromm M, Schulzke JD (2009) Barrier effects of nutritional factors. Ann NY Acad Sci 1165: 267–273

Aosasa S, Wells-Byrum D, Alexander JW, Ogle CK (2003) Influence of glutamine-supplemented caco-2 cells on cytokine production of mononuclear cells. JPEN J Parenter Enteral Nutr 27(5): 333–339

Ban H, Shigemitsu K, Yamatsuji T, Haisa M, Nakajo T, Takaoka M, Nobuhisa T, Gunduz M, Tanaka N, Naomoto Y (2004) Arginine and leucine regulate p70 s6 kinase and 4e-bp1 in intestinal epithelial cells. Int J Mol Med 13(4):537–543

Barbul A, Lazarou SA, Efron DT, Wasserkrug HL, Efron G (1990) Arginine enhances wound healing and lymphocyte immune responses in humans. Surgery 108(2):331–336 (discussion 336–337)

Bauchart-Thevret C, Cui L, Wu G, Burrin DG (2010) Arginine-induced stimulation of protein synthesis and survival in ipec-j2 cells is mediated by mTOR but not nitric oxide. Am J Physiol Endocrinol Metab 299(6):E899–E909

Belmonte L, Coeffier M, Le Pessot F, Miralles-Barrachina O, Hiron M, Leplingard A, Lemeland JF, Hecketsweiler B, Daveau M, Ducrotte P, Dechelotte P (2007) Effects of glutamine supplementation on gut barrier, glutathione content and acute phase response in malnourished rats during inflammatory shock. World J Gastroenterol 13(20):2833–2840

Boukhettala N, Leblond J, Claeyssens S, Faure M, Le Pessot F, Bole-Feysot C, Hassan A, Mettraux C, Vuichoud J, Lavoinne A, Breuille D, Dechelotte P, Coeffier M (2009) Methotrexate induces intestinal mucositis and alters gut protein metabolism independently of reduced food intake. Am J Physiol Endocrinol Metab 296(1):E182–E190

Boukhettala N, Ibrahim A, Claeyssens S, Faure M, Le Pessot F, Vuichoud J, Lavoinne A, Breuille D, Dechelotte P, Coeffier M (2010) A diet containing whey protein, glutamine, and TGFbeta modulates gut protein metabolism during chemotherapy-induced mucositis in rats. Dig Dis Sci 55(8):2172–2181

Boukhettala N, Claeyssens S, Bensifi M, Maurer B, Abed J, Lavoinne A, Dechelotte P, Coeffier M (2012) Effects of essential amino acids or glutamine deprivation on intestinal permeability and protein synthesis in HCT-8 cells: involvement of GCN2 and mTOR pathways. Amino Acids 42:375–383

Bouteloup C, Boirie Y, Dechelotte P, Gachon P, Beaufrere B (1998) Gut mucosal protein synthesis in fed and fasted humans. Am J Physiol 274(3 Pt 1):E541–E546

Bouteloup C, Claeyssens S, Maillot C, Lavoinne A, Lerebours E, Dechelotte P (2000) Effects of enteral glutamine on gut mucosal protein synthesis in healthy humans receiving glucocorticoids. Am J Physiol Gastrointest Liver Physiol 278(5):G677–G681

Bruins MJ, Soeters PB, Lamers WH, Deutz NE (2002) L-Arginine supplementation in pigs decreases liver protein turnover and increases hindquarter protein turnover both during and after endotoxemia. Am J Clin Nutr 75(6):1031–1044

Calder PC, Yaqoob P (1999) Glutamine and the immune system. Amino Acids 17(3):227–241

Claeyssens S, Lecleire S, Leblond J, Marion R, Hecketsweiler B, Lavoinne A, Ducrotte P, Dechelotte P, Coeffier M (2007) Lack of effect of acute enteral arginine infusion on whole-body and intestinal protein metabolism in humans. Dig Dis Sci 52(8):1826–1832

Coeffier M, Dechelotte P (2010) Combined infusion of glutamine and arginine: does it make sense? Curr Opin Clin Nutr Metab Care 13(1):70–74

Coeffier M, Miralles-Barrachina O, Le Pessot F, Lalaude O, Daveau M, Lavoinne A, Lerebours E, Dechelotte P (2001) Influence of glutamine on cytokine production by human gut in vitro. Cytokine 13(3):148–154

Coeffier M, Marion R, Leplingard A, Lerebours E, Ducrotte P, Dechelotte P (2002) Glutamine decreases interleukin-8 and interleukin-6 but not nitric oxide and prostaglandins e(2) production by human gut in vitro. Cytokine 18(2):92–97

Coeffier M, Claeyssens S, Hecketsweiler B, Lavoinne A, Ducrotte P, Dechelotte P (2003a) Enteral glutamine stimulates protein synthesis and decreases ubiquitin mRNA level in human gut mucosa. Am J Physiol Gastrointest Liver Physiol 285(2):G266–G273

Coeffier M, Marion R, Ducrotte P, Dechelotte P (2003b) Modulating effect of glutamine on IL-1beta-induced cytokine production by human gut. Clin Nutr 22(4):407–413

Coeffier M, Claeyssens S, Lecleire S, Leblond J, Coquard A, Bole-Feysot C, Lavoinne A, Ducrotte P, Dechelotte P (2008) Combined enteral infusion of glutamine, carbohydrates, and

antioxidants modulates gut protein metabolism in humans. Am J Clin Nutr 88(5):1284–1290

Coeffier M, Claeyssens S, Bensifi M, Lecleire S, Boukhettala N, Maurer B, Donnadieu N, Lavoinne A, Cailleux AF, Dechelotte P (2011) Influence of leucine on protein metabolism, phosphokinase expression, and cell proliferation in human duodenum. Am J Clin Nutr 93:1255–1262

Coëffier M, Claeyssens S, Bôle-Feysot C, Guérin C, Maurer B, Lecleire S, Coquard A, Lavoinne A, Cailleux A-F, Déchelotte P (2011) Un apport azoté stimule la synthèse protéique duodénale chez l'homme sain par un mécanisme indépendant de la voie mtor. Nutr Clin Métabol 25(Suppl 2):S36 (Abstract)

Corl BA, Odle J, Niu X, Moeser AJ, Gatlin LA, Phillips OT, Blikslager AT, Rhoads JM (2008) Arginine activates intestinal p70(s6k) and protein synthesis in piglet rotavirus enteritis. J Nutr 138(1):24–29

Cui XL, Iwasa M, Iwasa Y, Ohmori Y, Yamamoto A, Maeda H, Kume M, Ogoshi S, Yokoyama A, Sugawara T, Funada T (1999) Effects of dietary arginine supplementation on protein turnover and tissue protein synthesis in scald-burn rats. Nutrition 15(7–8):563–569

Dechelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coeffier M, Hecketsweiler B, Merle V, Mazerolles M, Samba D, Guillou YM, Petit J, Mansoor O, Colas G, Cohendy R, Barnoud D, Czernichow P, Bleichner G (2006) L-Alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: the french controlled, randomized, double-blind, multicenter study. Crit Care Med 34(3):598–604

Deniel N, Marion-Letellier R, Charlionet R, Tron F, Leprince J, Vaudry H, Ducrotte P, Dechelotte P, Thebault S (2007) Glutamine regulates the human epithelial intestinal HCT-8 cell proteome under apoptotic conditions. Mol Cell Proteomics 6(10):1671–1679

De-Souza DA, Greene LJ (2005) Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. Crit Care Med 33(5):1125–1135

El Yousfi M, Breuille D, Papet I, Blum S, Andre M, Mosoni L, Denis P, Buffiere C, Obled C (2003) Increased tissue protein synthesis during spontaneous inflammatory bowel disease in HLA-B27 rats. Clin Sci (Lond) 105(4):437–446

Gennari R, Alexander JW, Eaves-Pyles T (1995) Effect of different combinations of dietary additives on bacterial translocation and survival in gut-derived sepsis. JPEN J Parenter Enteral Nutr 19(4):319–325

Higashiguchi T, Hasselgren PO, Wagner K, Fischer JE (1993) Effect of glutamine on protein synthesis in isolated intestinal epithelial cells. JPEN J Parenter Enteral Nutr 17(4):307–314

Higashiguchi T, Noguchi Y, Meyer T, Fischer JE, Hasselgren PO (1995) Protein synthesis in isolated enterocytes from septic or endotoxaemic rats: regulation by glutamine. Clin Sci (Lond) 89(3):311–319

Holecek M, Muthny T, Kovarik M, Sispera L (2006) Simultaneous infusion of glutamine and branched-chain amino acids (BCAA) to septic rats does not have more favorable effect on protein synthesis in muscle, liver, and small intestine than separate infusions. JPEN J Parenter Enteral Nutr 30(6):467–473

Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG, van Leeuwen PA (1998) Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet 352(9130):772–776

Hubert-Buron A, Leblond J, Jacquot A, Ducrotte P, Dechelotte P, Coeffier M (2006) Glutamine pretreatment reduces IL-8 production in human intestinal epithelial cells by limiting IkappaB-alpha ubiquitination. J Nutr 136(6):1461–1465

Humbert B, Nguyen P, Dumon H, Deschamps JY, Darmaun D (2002) Does enteral glutamine modulate whole-body leucine kinetics in hypercatabolic dogs in a fed state? Metabolism 51(5):628–635

Kul M, Vurucu S, Demirkaya E, Tunc T, Aydinoz S, Meral C, Kesik V, Alpay F (2009) Enteral glutamine and/or arginine supplementation have favorable effects on oxidative stress parameters in neonatal rat intestine. J Pediatr Gastroenterol Nutr

Labow BI, Souba WW (2000) Glutamine. World J Surg 24(12): 1503–1513

Le Bacquer O, Nazih H, Blottiere H, Meynial-Denis D, Laboisse C, Darmaun D (2001) Effects of glutamine deprivation on protein synthesis in a model of human enterocytes in culture. Am J Physiol Gastrointest Liver Physiol 281(6):G1340–G1347

Le Bacquer O, Laboisse C, Darmaun D (2003) Glutamine preserves protein synthesis and paracellular permeability in caco-2 cells submitted to "Luminal fasting". Am J Physiol Gastrointest Liver Physiol 285(1):G128–G136

Lechowski S, Feilhauer K, Staib L, Coeffier M, Bischoff SC, Lorentz A (2012) Combined arginine and glutamine decrease release of de novo synthesized leukotrienes and expression of proinflammatory cytokines in activated human intestinal mast cells. Eur J Nutr

Lecleire S, Hassan A, Marion-Letellier R, Antonietti M, Savoye G, Bole-Feysot C, Lerebours E, Ducrotte P, Dechelotte P, Coeffier M (2008) Combined glutamine and arginine decrease proinflammatory cytokine production by biopsies from Crohn's patients in association with changes in nuclear factor-kappaB and p38 mitogen-activated protein kinase pathways. J Nutr 138(12):2481–2486

Lenaerts K, Renes J, Bouwman FG, Noben JP, Robben J, Smit E, Mariman EC (2007) Arginine deficiency in preconfluent intestinal caco-2 cells modulates expression of proteins involved in proliferation, apoptosis, and heat shock response. Proteomics 7(4):565–577

Leon P, Redmond HP, Stein TP, Shou J, Schluter MD, Kelly C, Lanza-Jacoby S, Daly JM (1991) Arginine supplementation improves histone and acute-phase protein synthesis during gram-negative sepsis in the rat. JPEN J Parenter Enteral Nutr 15(5):503–508

Li N, Lewis P, Samuelson D, Liboni K, Neu J (2004) Glutamine regulates caco-2 cell tight junction proteins. Am J Physiol Gastrointest Liver Physiol 287(3):G726–G733

Liboni KC, Li N, Scumpia PO, Neu J (2005) Glutamine modulates LPS-induced IL-8 production through ikappaB/NF-kappaB in human fetal and adult intestinal epithelium. J Nutr 135(2):245–251

Marchini JS, Nguyen P, Deschamps JY, Maugere P, Krempf M, Darmaun D (1999) Effect of intravenous glutamine on duodenal mucosa protein synthesis in healthy growing dogs. Am J Physiol 276(4 Pt 1):E747–E753

Marion R, Coeffier MM, Gargala G, Ducrotte P, Dechelotte PP (2004) Glutamine and CXC chemokines IL-8, Mig, IP-10 and I-TAC in human intestinal epithelial cells. Clin Nutr 23(4):579–585

Moinard C, Cynober L, de Bandt JP (2005) Polyamines: metabolism and implications in human diseases. Clin Nutr 24(2):184–197

Murgas Torrazza R, Suryawan A, Gazzaneo MC, Orellana RA, Frank JW, Nguyen HV, Fiorotto ML, El-Kadi S, Davis TA (2010) Leucine supplementation of a low-protein meal increases skeletal muscle and visceral tissue protein synthesis in neonatal pigs by stimulating mTOR-dependent translation initiation. J Nutr 140(12):2145–2152

Nakajo T, Yamatsuji T, Ban H, Shigemitsu K, Haisa M, Motoki T, Noma K, Nobuhisa T, Matsuoka J, Gunduz M, Yonezawa K, Tanaka N, Naomoto Y (2005) Glutamine is a key regulator for amino acid-controlled cell growth through the mTOR signaling pathway in rat intestinal epithelial cells. Biochem Biophys Res Commun 326(1):174–180

Nakshabendi IM, Downie S, Russell RI, Rennie MJ (1996) Increased rates of duodenal mucosal protein synthesis in vivo in patients with untreated coelia disease. Gut 39(2):176–179

Nieves C Jr, Langkamp-Henken B (2002) Arginine and immunity: a unique perspective. Biomed Pharmacother 56(10):471–482

Planas M, Schwartz S, Arbos MA, Farriol M (1993) Plasma glutamine levels in septic patients. JPEN J Parenter Enteral Nutr 17(3): 299–300

Rhoads MJ, Wu G (2009) Glutamine, arginine, and leucine signaling in the intestine. Amino Acids 37(1):111–122

Rhoads JM, Argenzio RA, Chen W, Rippe RA, Westwick JK, Cox AD, Berschneider HM, Brenner DA (1997) L-Glutamine stimulates intestinal cell proliferation and activates mitogen-activated protein kinases. Am J Physiol 272(5 Pt 1):G943–G953

Rhoads JM, Niu X, Odle J, Graves LM (2006) Role of mTOR signaling in intestinal cell migration. Am J Physiol Gastrointest Liver Physiol 291(3):G510–G517

Rhoads JM, Liu Y, Niu X, Surendran S, Wu G (2008) Arginine stimulates cdx2-transformed intestinal epithelial cell migration via a mechanism requiring both nitric oxide and phosphorylation of p70 s6 kinase. J Nutr 138(9):1652–1657

Rittler P, Schiefer B, Demmelmair H, Koletzko B, Roscher AA, Jacobs R, Krick M, Jauch KW, Hartl WH (2005) Effect of amino acid infusion on human postoperative colon protein synthesis in situ. JPEN J Parenter Enteral Nutr 29(4):255–261

Sakiyama T, Musch MW, Ropeleski MJ, Tsubouchi H, Chang EB (2009) Glutamine increases autophagy under basal and stressed conditions in intestinal epithelial cells. Gastroenterology 136(3):924–932

Samuels SE, Taillandier D, Aurousseau E, Cherel Y, Le Maho Y, Arnal M, Attaix D (1996) Gastrointestinal tract protein synthesis and mRNA levels for proteolytic systems in adult fasted rats. Am J Physiol 271(2 Pt 1):E232–E238

Sido B, Seel C, Hochlehnert A, Breitkreutz R, Droge W (2006) Low intestinal glutamine level and low glutaminase activity in Crohn's disease: a rational for glutamine supplementation? Dig Dis Sci 51(12):2170–2179

Singleton KD, Wischmeyer PE (2008) Glutamine attenuates inflammation and NF-kappaB activation via Cullin-1 deneddylation. Biochem Biophys Res Commun 373(3):445–449

Tan B, Yin Y, Kong X, Li P, Li X, Gao H, Huang R, Wu G (2010) L-Arginine stimulates proliferation and prevents endotoxin-induced death of intestinal cells. Amino Acids 38(4):1227–1235

Tandon BN, Magotra ML, Saraya AK, Ramalingaswami V (1968) Small intestine in protein malnutrition. Am J Clin Nutr 21(8):813–819

Tannus AF, Darmaun D, Ribas DF, Oliveira JE, Marchini JS (2009) Glutamine supplementation does not improve protein synthesis rate by the jejunal mucosa of the malnourished rat. Nutr Res 29(8):596–601

Thebault S, Deniel N, Marion R, Charlionet R, Tron F, Cosquer D, Leprince J, Vaudry H, Ducrotte P, Dechelotte P (2006) Proteomic analysis of glutamine-treated human intestinal epithelial HCT-8 cells under basal and inflammatory conditions. Proteomics 6(13):3926–3937

Turner JR (2009) Intestinal mucosal barrier function in health and disease. Nat Rev Immunol 9(11):799–809

van der Hulst RR, van Kreel BK, von Meyenfeldt MF, Brummer RJ, Arends JW, Deutz NE, Soeters PB (1993) Glutamine and the preservation of gut integrity. Lancet 341(8857):1363–1365

Vermeulen MA, de Jong J, Vaessen MJ, van Leeuwen PA, Houdijk AP (2011) Glutamate reduces experimental intestinal hyperpermeability and facilitates glutamine support of gut integrity. World J Gastroenterol 17(12):1569–1573

Winter TA, O'Keefe SJ, Callanan M, Marks T (2007) Effect of severe undernutrition and subsequent refeeding on gut mucosal protein fractional synthesis in human subjects. Nutrition 23(1):29–35

Wu G (2009) Amino acids: metabolism, functions, and nutrition. Amino Acids 37(1):1–17

Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, Carey Satterfield M, Smith SB, Spencer TE, Yin Y (2009) Arginine metabolism and nutrition in growth, health and disease. Amino Acids 37(1):153–168

Xi P, Jiang Z, Dai Z, Li X, Yao K, Zheng C, Lin Y, Wang J, Wu G (2012) Regulation of protein turnover by L-glutamine in porcine intestinal epithelial cells. J Nutr Biochem

Yin Y, Yao K, Liu Z, Gong M, Ruan Z, Deng D, Tan B, Wu G (2010) Supplementing L-leucine to a low-protein diet increases tissue protein synthesis in weanling pigs. Amino Acids 39(5):1477–1486

Zhou Q, Souba WW, Croce CM, Verne GN (2010) MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. Gut 59(6):775–784