Invited commentary

Is there a requirement for glutamine catabolism in the small intestine?

A search for 'glutamine' will yield over 20 000 hits on the World Wide Web, many related to the use of glutamine as a dietary supplement. Although glutamine is not, in the traditional sense, an essential amino acid, its use in clinical settings and by the general public has steadily increased over the past 10 years. The rationale for dietary glutamine supplements is based, in part, on its role as a fuel for the gastrointestinal tract and the immune system, and the perceived need to maintain high levels of glutamine in skeletal muscle to minimize proteolysis and maximize protein synthesis. In addition, glutamine is a major substrate for renal NH_3 production, hepatic urea synthesis, and both renal and hepatic gluconeogenesis, and the amide N of glutamine is required for the synthesis of purines, pyrimidines and glucosamine. The results of glutamine supplementation in pathological states have not always been unequivocal but significant benefits have been reported in patients undergoing bone marrow transplantation, in patients with various gastrointestinal tract disorders, and in the critically ill (Griffiths *et al.* 1997; Furst, 1998).

Given the explosion of reports involving the use of glutamine it is perhaps surprising how little we really know regarding whole-body glutamine homeostasis in species other than the rat. In this issue of the *British Journal of Nutrition*, Gate *et al.* (1999) describe the utilization, and fate, of arterial glutamine metabolized by the portal-drained viscera (PDV) of lambs starved for 24 h. Their results are interesting and provocative, not only in terms of ruminant biology, but also with regard to our understanding of glutamine homeostasis in general.

The requirement for high levels of glutamine by certain cell types, such as mammalian cells in culture, the small-intestinal epithelium and immune cells has often been explained by a need for large amounts of glutamine for macromolecule synthesis but this accounts for < 4 % glutamine utilized (Newsholme *et al.* 1985). The realization that glutamine was the principal respiratory fuel of the rat small-intestinal mucosa (Neptune, 1965; Windmueller & Spaeth, 1974) explained the purpose of high rates of glutamine metabolism but did not answer the question, why glutamine? However, based on the data from the rat, it soon became dogma that the small-intestine epithelial mucosa had an absolute requirement for high rates of glutamine catabolism. Interestingly, in their original papers Windmueller and colleagues (Windmueller & Spaeth, 1974; Pinkus & Windmueller, 1977) showed that although there was net glutamine use by the PDV of the rat, dog and some other species, there was net glutamine output across the gut of guinea-pig and chicken. Similar species differences were seen in the intestinal expression of phosphate-activated glutaminase (*EC* 3.5.1.2) (Pinkus & Windmueller, 1977; Wu *et al.* 1998).

Despite the early recognition of species differences in small-intestine glutamine metabolism little attention has been paid to what such differences mean. Similarly, the suitability of inferring patterns of glutamine metabolism in one species from data obtained in other species has not been widely questioned. In ruminants the elegant chronic catheterization studies of Bergman and colleagues (Heitmann & Bergman, 1978) demonstrated net glutamine uptake by sheep PDV. Although these results were never directly compared with those for other species, on examination they do suggest lower rates of glutamine utilization by the PDV of ruminants. Gate *et al.* (1999) have used a double catheterization technique (portal vein and mesenteric vein) combined with the use of 5-^{15}N-labelled glutamine to follow the fate of glutamine metabolized by lamb PDV. Their results clearly show that the rate of turnover of plasma glutamine is lower in the lamb than in single-stomached species such as man, pig and rat (see van Acker *et al.* 1998). In keeping with previous reports they did find net glutamine uptake across the PDV and this accounted for 45 % of the total plasma turnover. However, most of the glutamine was used by non-mesenteric-vein drained tissues, not the small intestine. Although interpretation of the results is limited due to a small release of glutamine which could be due to *de novo* synthesis or absorption from the lumen, this study nevertheless indicates relatively low reliance on glutamine metabolism by ruminant PDV.

Perhaps the most interesting finding of the work of Gate *et al.* (1999) is the fate of the glutamine taken up by lamb PDV. Windmueller & Spaeth (1974) accounted for all of the glutamine N utilized by intact rat small intestine by the production of NH_3 and various amino acid end-products. Although this left no room for glutamine incorporation into macromolecules it probably reflects the limits of accuracy of the methodology in the rat, given such large differences in flux between energy production and biosynthetic pathways. In the lamb Gate *et al.* (1999) found that only 24 % of the glutamine amide N taken up across the mesenteric-drained viscera (small intestine) was released as NH_3 (a crude estimate of the amount of glutamine used for energy provision). The majority of the glutamine taken up was found in protein (84 %), RNA (3·6 %) and DNA (2·1 %), with less as NH_3 and more as macromolecules in the non-mesenteric-drained tissues. Thus, in the 24-h-starved lamb, arterial glutamine is utilized by the

PDV primarily for macromolecule synthesis not for energy production.

These findings of low rates of glutamine turnover and utilization (for energy production) by the PDV of ruminants questions the requirement of the small-intestinal mucosa for glutamine as a fuel. As mentioned earlier, species such as the chicken and guinea-pig show net glutamine output across the PDV. Furthermore, in the rat, intestinal glutamine utilization can be replaced by ketone-body oxidation during starvation or diabetes (Windmueller & Spaeth, 1974; Watford *et al.* 1987). However, Reeds and colleagues (Reeds *et al.* 1996; Burrin & Reeds 1997) have gone so far as to question the need for glutamine catabolism in the small-intestine. From their work on pigs, they suggest that dietary glutamate is the principal fuel of the small-intestinal mucosa. If true, this would ensure that 100 % of this abundant dietary amino acid is metabolized during absorption and thus maintains low glutamate levels in the circulation. This explanation would relegate glutamine to a 'back up' fuel, used when the intestinal lumen is empty, a relatively quiescent state. An additional explanation for high rates of glutamine (and glutamate) metabolism in the intestine is related to the handling of dietary protein. Halperin and colleagues (Jungas *et al.* 1992; Halperin & Rolleston, 1993) calculated the energy balance involved in the metabolism of an average human daily protein intake based on known tissue-specific metabolism of amino acids. They found that if the amino acids metabolized in the liver were to undergo complete oxidation in that organ the O_2 required would be equal to, or exceed, the known daily hepatic O_2 consumption. Thus, amino acids are only partially oxidized in the liver and they reasoned that the pathways to the end-products, glucose (some ketones) and urea, could be viewed as ATP utilizing–ADP regenerating systems which allow the continued catabolism of dietary amino acids. In this scenario the metabolism of dietary glutamine and glutamate in the small intestine before entry into the portal vein becomes a mechanism to reduce the ATP-generating load arriving at the liver after a meal and so permit the liver rapidly to dispose of the excess amino acids (Halperin & Rolleston, 1993; Watford, 1994). In other words, small-intestinal cells utilize glutamate and glutamine primarily in response to dietary protein intake and not because of any innate need of the cell. Of course, these explanations do not explain why other cell types also show high rates of glutamine utilization and they do not allow judgement as to the efficacy of glutamine or other substrates as supplements in pathological conditions.

Thus, the findings of low rates of glutamine utilization for energy production in ruminant small intestine raises a number of questions about interorgan glutamine metabolism in ruminants; but it also questions the requirement for high rates of glutamine catabolism by small-intestinal cells in general. The work clearly reminds us not to extrapolate too much from one model species and that good comparative biology can often support, or challenge, our long-held beliefs.

Malcolm Watford
Department of Nutritional Sciences
Cook College
Rutgers University
New Brunswick NJ 08901
USA

References

Burrin DG & Reeds PJ (1997) Alternative fuels in the gastrointestinal tract. *Current Opinion in Gastroenterology* **13**, 165–170.

Furst P (1998) Old and new substrates in clinical nutrition. *Journal of Nutrition* **128**, 789–796.

Gate JJ, Parker DS & Lobley GE (1999) The metabolic fate of the amido-N group of glutamine in the tissues of the gastrointestinal tract in 24 h fasted sheep. *British Journal of Nutrition* **81**, 297–306.

Griffiths RD, Jones C & Palmer TEA (1997) Six month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* **13**, 295–302.

Halperin MJ & Rolleston FS (1993) In *Clinical Detective Stories*, pp. 242–243. London: Portland Press.

Heitmann RN & Bergman EN (1978) Glutamine metabolism, interorgan transport, and glucogenicity in the sheep. *American Journal of Physiology* **234**, E197–E203.

Jungas RL, Halperin ML & Brosnan JT (1992) Quantitative analysis of amino acid oxidation and related gluconeogenesis in humans. *Physiological Reviews* **72**, 419–448.

Neptune EM (1965) Respiration and oxidation of various substrates by ileum in vivo. *American Journal of Physiology* **209**, 329–332.

Newsholme EA, Crabtree B & Ardawi MSM (1985) Glutamine metabolism in lymphocytes: its biochemical, physiological and clinical importance. *Quarterly Journal of Experimental Physiology* **70**, 473–489.

Pinkus LM & Windmueller HG (1977) Phosphate-dependent glutaminase of small intestine: localization and role in intestinal glutamine metabolism. *Archives of Biochemistry and Biophysics* **182**, 506–517.

Reeds PJ, Burrin DG, Jahoor F, Wykes L, Henry J & Frazer EM (1996) Enteral glutamate is almost completely metabolized in first pass by the gastrointestinal tract of infant piglets. *American Journal of Physiology* **270**, E413–E418.

Van Acker BA, Hulsewe KW, Wagenmakers AJ, Deutz NE, van Kreel BK, Halliday D, Matthews DE, Soeters PB & von Meyenfeldt MF (1998) Absence of glutamine isotope steady state: implications for the assessment of whole-body glutamine production rate. *Clinical Science* **95**, 339–346.

Watford M (1994) Glutamine metabolism in rat small intestine: synthesis of three-carbon products in isolated enterocytes. *Biochimica et Biophysica Acta* **1200**, 73–78.

Watford M, Erbelding EJ & Smith EM (1987) The regulation of glutamine and ketone body metabolism in the small intestine of the long-term (40 day) streptozotocin-diabetic rat. *Biochemical Journal* **242**, 61–68.

Windmueller HG & Spaeth AE (1974) Uptake and metabolism of plasma glutamine by the small intestine. *Journal of Biological Chemistry* **249**, 5070–5079.

Wu G, Chung-Bok M-I, Vincent N, Kowalski TJ, Choi Y-E & Watford M (1998) Distribution of phosphate-activated glutaminase isozymes in the chicken. *Comparative Biochemistry and Physiology* **120**B, 285–290.