Glutamine and the Bowel$^{1,2}$

Peter J. Reeds$^3$ and Douglas G. Burrin*  

Department of Animal Sciences, University of Illinois, Urbana, IL 61801 and *U.S. Department of Agriculture/ARS Children’s Nutrition Research Center, Baylor College of Medicine, Houston, TX

ABSTRACT Since the pioneering work of Windmueller and Spaeth, the importance of glutamine to the support of intestinal mucosal metabolic function has become generally accepted. Nevertheless, the mechanisms underlying this role still remain obscure. This paper explores a number of questions: 1) Is glutamine essential for intestinal function? 2) To what extent does this relate to its intermediary metabolism? 3) What is the importance of glutamine as a biosynthetic precursor? 4) Is glutamine supplementation of the nutrient mixture presented to patients of any metabolic or clinical benefit? As a result of this exploratory exercise, the following general conclusions were reached: 1) Much suggestive biochemical and physiologic evidence exists that implies that glutamine, especially systemic glutamine, supports the function of the intestinal mucosal system. 2) Despite the extensive metabolism of this amino acid by the intestinal tissues, most evidence suggests that if glutamine does play a physiologic role in the bowel, it is not compellingly related to its intermediary metabolism. 3) There is, on the other hand, evidence that the mucosal cells not only utilize extracellular glutamine but synthesize the amino acid. Given that inhibition of glutamine synthesis inhibits both proliferation and differentiation of mucosal cell cultures, this suggests some more subtle regulatory role. This notion is supported by the demonstration that glutamine will activate a number of genes associated with cell cycle progression in the mucosa. 4) Despite the accumulated evidence, the mechanisms underlying glutamine’s function and the question whether glutamine supplementation uniformly benefits mucosal health remain equivocal at best. J. Nutr. 131: 2505S–2508S, 2001.

KEY WORDS: • glutamine metabolism • intestine • glutamate

The traditional view of the intestine has focused on its function as an organ of digestion, nutrient absorption and fermentation. However, it has become very clear that the intestine is a complex, multicellular organ that performs a number of critical physiologic functions that are separate from its role in nutrient assimilation. Thus, the intestinal mucosa contains secretory, immune and neuroendocrine cells in addition to the absorptive enterocytes. As such, the intestinal tissues are involved in immune surveillance and in generating endocrine responses to the luminal environment (Burrin et al. 2000). These regulatory roles are supported by an intrinsic intestinal neural system (Kudsk 2000) that is separate from, but functionally related to the central neural pathways. Thus, the intestine is one partner in a central-peripheral system that senses both the antigenic and the nutritional environment and thereby modifies the host response.

The host pays a metabolic price for these critical intestinal functions. The portal drained viscera (the stomach, intestine, pancreas and spleen) are among the most metabolically active tissues in the body. For example, although these tissues collectively never account for >6% of body weight, they can be responsible for up to 50% of the whole-body turnover of some essential amino acids (Stoll et al. 1998, Yu et al. 1992 and 1995) and between 10 and 20% of whole-body energy expenditure (van Goudoever et al. 2000). For these reasons alone, the examination of the substrates that are used by the intestinal tissues and the potential for nutrient regulation of the intestine’s multiple functions is a subject worthy of intensive study.

In 1974, Windmueller and Spaeth published the first of a series of highly influential papers (Windmueller and Spaeth 1974, 1975, 1976 and 1980) in which they demonstrated that amino acids, especially nonessential amino acids have an important metabolic role in the intestine. However, from the perspective of the present discussion, they made the crucial observation that the intestine removes as much as 25% of the systemic flux of glutamine. Their measurements of intestinal glutamine metabolism also showed that glutamine metabolism could not only contribute a nutritionally important portion of intestinal energy generation, but that the amino acid was the precursor for a number of important metabolic pathways, especially those leading to the synthesis of ornithine, citrulline,
TABLE 1

Pathways supported by the amido-N of glutamine and by glutamine intermediary metabolism in the intestinal mucosa

<table>
<thead>
<tr>
<th>Amido-N end products</th>
<th>Intermediary metabolic products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purine</td>
<td>Ornithine</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td>Arginine</td>
</tr>
<tr>
<td>Amino sugars</td>
<td>Proline</td>
</tr>
<tr>
<td></td>
<td>Polyamines</td>
</tr>
<tr>
<td></td>
<td>Ammonia</td>
</tr>
<tr>
<td></td>
<td>Alanine</td>
</tr>
</tbody>
</table>

1 Catabolic end products released to the liver and used in urea synthesis.

New roles for glutamine in the gut

Despite the conclusion that we reached in the previous section, there is increasing evidence that favors not only a specific role for glutamine but also the idea that this role may not be strictly metabolic. The first evidence is the crucially important observation that extracellular glutamine is not only removed from the arterial circulation by the intestinal tissues, but that the mucosal cells in both the crypt and villous compartments are simultaneously synthesizing glutamine. Thus, Neu and his colleagues (Shenoy et al. 1996) published immunocytochemical evidence for the presence of glutamine synthase in the mucosa, and James et al. (1998) demonstrated the presence of the enzyme by direct biochemical measure:

Fig. 1

**FIGURE 1** Metabolic interrelationships among amino acids in isolated enterocytes. Porcine enterocytes were isolated and incubated in a complete medium containing [U-13C]glutamate, glutamine, glucose or proline. The data are the proportion of the intracellular flux of their potential products. (Unpublished data of G. Wu and P. J. Reeds.)
flow and arterial and portal 13CO2 concentrations and isotopic enrich-
ments were measured. Values are the proportion of total visceral CO2
production attributable to the respective substrates. [Data from Stoll et
al. (1999) and S. Van der Schoor unpublished.]

FIGURE 2 Contributors to intestinal CO2 production in well-nour-
ished piglets. Pigs (8 kg) were catheterized in the carotid artery and the
jugular and hepatic portal veins. Pigs were fed by intragastric diet
infusion and were given enteral [U-13C] glutamate or [1-13C] leucine or
flow and arterial and portal 13CO2 concentrations and isotopic enrich-
ments were measured. Values are the proportion of total visceral CO2
production attributable to the respective substrates. [Data from Stoll et
al. (1999) and S. Van der Schoor unpublished.]

Does glutamine make a difference?

When the evidence that suggests a specific role for glu-
tamine in the bowel is taken with the alterations in interorgan
flow of glutamine (Soubia and Austgen 1990) and intestinal
protective function (Stechmiller et al. 1997) that accompany
disease and stress, it is plausible to argue that glutamine
supplementation may be of therapeutic benefit in the support
of the intestinal mucosa and immune systems (Wilmore and
Shabert 1998) under conditions of disease and trauma. Not
surprisingly, there have been many attempts to use glutamine
supplementation to ameliorate the metabolic changes that
accompany stress in general and intestinal disease in particular
[reviewed by Elia and Lunn (1997), Fürst (2000) and Sacks
(1999)].

We think that it is fair to say that not only does the
literature report confusing and variable success but also serves
to emphasize the following. First, it is crucial to identify the
desired end point of glutamine supplementation. Second, it is
equally important to define the nature of the stress or disease
that it is hoped will be ameliorated with glutamine. Third, it
is more than likely that the route of glutamine supplementation
(parenteral or enteral) influences the response and, fi-
nally, other aspects of the nutritional support of the patient are
of extreme importance.

Among these considerations, we would argue that the ques-
tion of end point is the most crucial, and the effects of
glutamine on nitrogen metabolism provide a good example of
this. Thus, in the eight studies of parenteral glutamine sup-
plementation identified by Sacks (1999) in which measure-
ments of nitrogen balance were made, there were uniform
increases in circulating glutamine concentrations and im-
proved nitrogen balance. On the other hand, clinically de-
monstrable benefit was not a uniform finding. Conversely,
in 18 studies of enteral glutamine supplementation (Fürst 2000),
there are no reports of significantly improved nitrogen bal-
ance, but a number of reports of improved morbidity. Even so,
the benefits have not been uniform (Elia and Lunn 1997). By
and large, we would conclude that effects of glutamine sup-
plements on mucosal mass, even in animal models, have been
equivocal at best.

Despite this rather negative conclusion, the emergence of
new roles for glutamine suggests other areas in which glu-
tamine supplements may prove to be of benefit. In this regard,
one promising area is the putative role of glutamine in amino
sugar synthesis. This role has two potential implications. First,
by influencing the synthesis of components of the extracellular
matrix, glutamine may be one factor in the maintenance of
mucosal structure, especially the maintenance of tight junc-
tions (Panigrahi et al. 1997). Second, by being a potential
precursor for N-acetylglucosamine and N-acetylgalactosamine
synthesis, glutamine could play a critical role in intestinal
mucin synthesis and hence in the maintenance of the passive
barrier to bacterial ingress (Khan et al. 1999). In this regard,
one of the most interesting recent papers concerned with
enteral glutamine supplementation of the diets of low-birth
weight infants (Neu et al. 1997), the supplement had no effect on
either circulating glutamine concentrations or infant
growth but was associated with changes in immune cell sub-
type distribution that were compatible with the idea that the
supplement had lowered the overall immune challenge pre-
sented to the infants. Whether this reflected the maintenance
of tight junctions and mucin synthesis (Khan et al. 1999) or
whether it reflected interactions with locally generated cyto-
kines (Kudsk et al. 2000) is not known at this time.

CONCLUSIONS

We have sought to make three main points. First, there is
much suggestive biochemical and physiologic evidence that
glutamine, especially systemic glutamine, supports the func-
tion of the intestinal mucosal system. Second, despite the
extensive metabolism of this amino acid by the intestinal
tissues, most evidence suggests that if glutamine does play a
physiologic role in the bowel, it is in a way compellingly related to
its intermediary metabolism. In fact, glutamate and proline,
especially derived from the diet, can readily substitute for
many of the metabolic roles of glutamine, including energy
generation and amino acid synthesis. Third, there is, on the other hand, evidence that the mucosal cells not only utilize extracellular glutamine but also synthesize the amino acid. Given that inhibition of glutamine synthesis inhibits both proliferation and differentiation of mucosal cell cultures, it seems that glutamine may be performing some more subtle regulatory role. This notion is supported by the demonstration that glutamine will activate a number of genes associated with cell cycle progression in the mucosal cells. However, despite the accumulated evidence, both the mechanism underlying glutamine’s function and whether glutamine supplementation uniformly benefits mucosal health remain, at best, equivocal.

LITERATURE CITED


