

The Impact of Enteral Insulin-Like Growth Factor 1 and Nutrition on Gut Permeability and Amino Acid Utilization^{1,2}

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Abstract

The intestine serves numerous purposes. In addition to digestion and absorption, the intestine functions as an organ that provides specific and nonspecific protection against pathological bacteria and noxious agents. At birth, and certainly when birth occurs prematurely, these functions are not yet fully developed. This article addresses the specific needs of the neonatal gut to perform these functions adequately and describes efforts to modulate intestinal barrier function by preterm formula supplemented with insulin-like growth factor 1. J. Nutr. 138: 1829S–1833S, 2008.

Introduction

The human intestine serves several important functions. Not only is it critical for the digestion of food and the assimilation of nutrients, but it is continually exposed to dietary toxins and pathogens and hence plays a crucial protective role. Furthermore, by virtue of the fact that it is exposed directly to the diet, the intestinal tract, especially the neural and neuroendocrine cells within the small intestinal villous structures, probably plays a critical role in coordinating the activity of its accessory organs and associated ingestive behavior (1). It is important to recognize also that the gut is a multicellular organ. The villus epithelium contains at least 4 distinct cell types, and ~70% of the total immune cell population resides either within the villus or in the Peyer's patches. Moreover, the gut contains an extensive and intrinsic neural system that is to some extent functionally independent of the central nervous system. Accordingly, the multicellular mucosa plays a key role in immune surveillance, in host protection against both toxins and pathogenic organisms, and in the transfer of information about the scale and composition of the diet to other components of the body. Finally, the intestinal tissues and other organs that collectively make up the portal-drained viscera (PDV)³

have an unusually high rate of energy expenditure, proliferation, protein synthesis, and secretion.

It is hardly surprising that this multiplicity of functions imposes a substantial nutritional cost on the organism. Much research shows that amino acids play a critical and probably specific role in the support of gut intermediary metabolism, secretion, and absorptive and protective functions (2–9). Thus, amino acid metabolism within the gastrointestinal (GI) tract and its accessory organs makes a disproportionate contribution to amino acid turnover and can have an important bearing on the availability of amino acids for the support of other functions such as growth and development.

Preterm birth and gut development

By 20 wk of gestation, the anatomic differentiation of the fetal gut has progressed to the extent that it resembles that of a newborn. Secretory and absorptive functions, however, develop at different rates; the intestinal absorptive process is only partially available before 26 wk of gestation, whereas gastric and pancreatic secretion is only basal and can be stimulated only partially even in the full-term newborn period (10).

Maturation of GI function in neonates is stimulated by enteral nutrition, whereas parenteral nutrition induces GI atrophy and malfunction (11–13). The effects of nutritional regimen on the maturation of the gut epithelium in neonates depend on gestational age at birth (14). Gut flora is influenced by gestational age as well, among other factors such as mode of delivery, local environment, type of feeding, and antibiotic treatment (15–17). Intestinal bacterial colonization with beneficial bacteria is delayed in preterm infants. The number of potentially pathogenic bacteria is high (18). This puts the preterm infant at a particular high risk because the gut is not yet fully developed and is permeable to the different pathogenic bacteria leading to sepsis. A major factor in the prevention of neonatal infections in the preterm neonate might therefore be the induction of increased permeability of the gut.

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³ Abbreviations used: GI, gastrointestinal; IGF, insulin-like growth factor; PDV, portal-drained viscera.

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The effect of insulin-like growth factor 1 on neonatal gut permeability

A possible cause for the increased permeability of the preterm intestine is that junctional proteins such as occludin and claudins, which form the adhesion and sealing between the epithelial cells, are not completely expressed as yet (19,20). Another manifestation of immaturity is the decreased activity of several digestive enzymes such as the pancreatic secretions (21). Enteral feeding is thought to be a natural stimulus for intestinal growth (22,23). But, in addition to the route of administration, the modality of nutrition is also important. Infants fed human milk have a lower incidence of GI-related disease than their formula-fed peers, indicating a protective effect of human milk (24,25). In addition, human-milk-fed infants show better intestinal growth and maturation (23). Bioactive compounds in breast milk are most likely responsible for these beneficial effects. Several growth factors that could account for this effect have been identified in the breast milk of mammals. For example epidermal growth factor, insulin-like growth factor (IGF), and peptides are found in human milk. Recently, much effort has been made to determine the effects of IGF-1 on intestinal function in newborn animals. IGF-1 is thought to be, in addition to a growth factor, also an antiapoptotic factor (26). The intestinal growth-enhancing effect of parenteral or subcutaneous administration of this single-chain polypeptide has been confirmed in numerous animal studies (27–29). Several other studies conducted to investigate the effects of enterally administered IGF-1 (30–35) show conflicting results. Increased intestinal growth was found in newborn piglets (31), whereas no effect of enterally administered IGF-1 was found in rats (32). We designed a randomized controlled study to assess the effects of enteral IGF-1 administration in slightly higher amounts than found in human colostrum to 60 premature human neonates (36). We hypothesized that IGF-1 would enhance gut function and development. To measure effects of IGF-1 on gut maturation and gut permeability, we performed weekly sugar absorption tests until the supplementation was stopped at 28 d postnatal age. **Figure 1** shows a gradual decline in the lactulose/mannitol ratio over time, indicating an improvement in intestinal barrier function as

the infant grows older and receives more enteral nutrition. Lactase activity, expressed as lactulose:lactose ratio, increased in time as expected (**Fig. 2**). The lower urinary lactose excretion resulted in the increase in the ratio because both molecules have the same molecular weight and size. Except for a small significant difference in lactulose:mannitol ratio indicative of a slightly lower permeability at postnatal d 14, no significant differences were observed between the IGF-1-supplemented group and the control group. We concluded that we could not really detect a beneficial effect of adding IGF-1 in this dosage to the formula of preterm infants during the first month of life.

Amino acid utilization

Another important issue, next to permeability in gut health, is the scale of amino acid utilization by the gut. In **Table 1** we summarize the data on intestinal amino acid utilization in the piglet and on first-pass splanchnic amino acid utilization in the human neonate. These data show that at least 40% of the total protein intake is used in the splanchnic bed, the large majority by the gut (37). They also show marked variation in the degree to which different amino acids are utilized, so that intestinal metabolism substantially modifies the mixture of amino acids available to the organism. Indeed, virtually all the dietary glutamate and aspartate are metabolized in first pass, in addition to the well-established utilization of arterial glutamine by the intestinal mucosa (38–40).

The second striking finding is that in the fed state, there is simultaneous utilization of both arterial and luminal essential amino acids by the intestinal tissues (3,41). In quantitative terms, arterial essential amino acids provide the majority of amino acids for metabolism in the PDV. This observation alone raises important issues with regard to the regulation of amino acid transport from the mesenteric artery to the intestinal mucosa, and it is regrettable that so little is known about the nature of the amino acid transporters on the basolateral membrane of the enterocytes.

The third important observation is the compartmentation of mucosal amino acid metabolism. We have already alluded to the fact that the majority of the essential amino acids utilized by the PDV as a whole are supplied from the mesenteric artery.

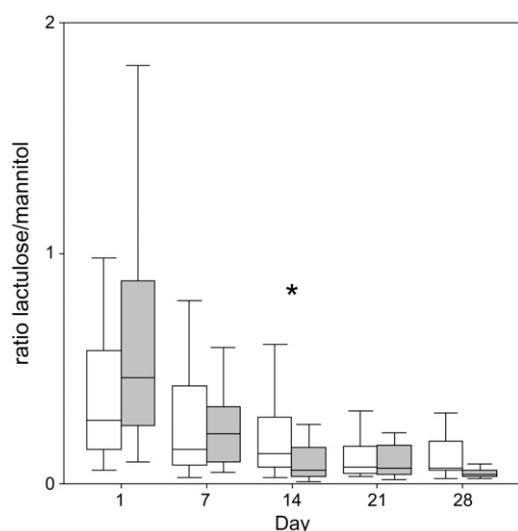


FIGURE 1 Urinary lactulose:mannitol ratio of preterm infants receiving either IGF-1 supplementation (gray bars) or placebo (white bars) for up to 4 wk. Values are means $\pm$ SD, $n = 30$. *Groups differ, $P = 0.022$. Reproduced with permission from (36).

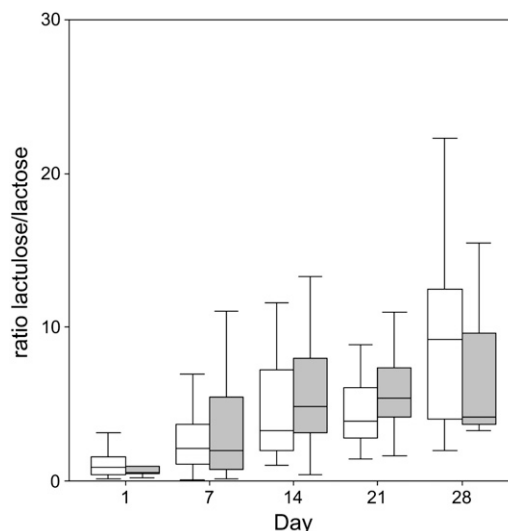


FIGURE 2 Urinary lactulose:lactose excretion in preterm infants supplemented with either enteral IGF-1 (gray bars) or placebo (white bars) for up to 4 wk. Values are means $\pm$ SD, $n = 30$. Reproduced with permission from (36).

TABLE 1 Intestinal (splanchnic) utilization of dietary amino acids in neonates¹

Amino acid	Neonatal pig	Human neonate
	% intake	
Leucine	53	48
Lysine	41	18
Threonine	85	70
Glutamine	67	46
Glutamate	96	74

¹ Data from various references (3,9,41,44,49,57,58).

However, data from humans (42), piglets (43,44), and sheep (45) reveal that there is channeling of newly transported arterial amino acids to mucosal protein synthesis, although we found recently that dietary threonine was the predominant source of duodenal protein synthesis in piglets (3). In contrast, intestinal intermediary metabolism, including energy generation (6) and glutathione (46) and amino acid synthesis (47,48), preferentially utilizes dietary amino acids as precursors. It follows from this that interactions between nutrition and intestinal disease, on one hand, and the impact of intestinal metabolism on host amino acid dynamics, on the other, are likely to be complex. For example, we have shown recently that restriction of dietary intake has little effect on the absolute first-pass intestinal metabolism of dietary lysine in human neonates (49) but suppresses the utilization of arterial amino acids such as threonine in neonatal pigs. Even so, the ingestion of low-protein diets is associated with a very substantial fall in the portal availability of some essential amino acids, notably lysine and threonine. In other words, the failure of low-protein diets to support peripheral tissue protein deposition is primarily a reflection of the nearly complete utilization of the dietary amino acids by the gut itself (3). It is not surprising then that a number of studies (50) show preservation of gut growth under nutritional conditions that markedly slow muscle growth.

Two critical questions are raised by these observations. What are the processes that consume such high quantities of amino acids, and what are the factors, if any, that regulate these processes? Answering both questions is important not only from the perspective of physiological understanding in the broadest sense but also from the perspective of the influence of the gut on the amino acid requirements of the organism as a whole.

A major issue regarding both questions is protein secretion in the intestine. It is almost a truism that the intestinal tissues in general, and small intestinal mucosa in particular, have a high rate of protein synthesis. Perhaps of more functional importance is the likelihood (at present not formally quantified) that a high proportion of this protein synthetic activity is devoted to secretory protein synthesis. Our data suggest that at least one-third of total visceral protein synthesis is secreted (37). Because total intestinal amino acid utilization can account for 50% of whole-body amino acid utilization, secretory protein synthesis both in the gut and in the pancreas is of substantial quantitative impact on amino acid dynamics. Clearly, such a rate of loss (which approaches the total amino acid intake in magnitude) could not be sustained, so an important issue, in relation to amino acid requirements, is the degree to which these secretions are recycled to the body. Indeed, on the basis of the relatively sparse information currently available, nonrecycled GI secretions could account for 30% of total basal amino acid requirements, and for threonine, it has been calculated that 60% or more of the maintenance requirement could be lost from the

ileum to the large bowel (51). Threonine requirement of newborn piglets maintained by parenteral nutrition is less than half that of enterally nourished animals (52). The critical point is that most of the amino acids passing to secretory protein synthesis are derived from the mesenteric artery. Thus, whether gut utilization of arterial amino acids is, or is not, regulated, either by systemic hormones or perhaps by regulatory peptides derived from the gut itself, remains a critically important issue.

The second important function of amino acids in the gut is as an energy source. Data extending back for at least 25 y strongly suggest that glutamate and aspartate of dietary origin and glutamine of systemic origin account for the majority of the energy generated in the small intestine. In addition, we have shown that under high-protein feeding conditions, the intestinal tissues also oxidize essential amino acids, including lysine (40,41). Remarkably, despite the fact that in the fed state the intestine releases large quantities of alanine and lactate to the portal circulation, dietary glucose plays virtually no role in intestinal metabolism (40). Furthermore, even though the PDV utilize considerable quantities of arterial glucose, perhaps as much as 30% of whole-body glucose turnover, the majority of this appears to be devoted to anabolic purposes, and less than a third is oxidized (53).

Finally, it is now clear that amino acids, notably glutamine, aspartate, glycine, and glutamate, are involved in a variety of biosynthetic functions in the intestine. These include the synthesis of nucleotides destined for RNA and DNA synthesis (54), the synthesis of citrulline, arginine, and proline (55), and of glutathione (46) and other regulatory compounds such as the polyamines. The extent to which these metabolic activities, all of which are vitally involved in other aspects of metabolic and protective function, can become compromised under conditions of inadequate amino acid nutrition presents an important but largely unanswered question. However, their potential importance is well illustrated by the derangements of both amino acid metabolism (56) and gut-protective mechanisms that accompany parenteral nutrition.

It is clear, therefore, that the intestine as a whole and the complex multicellular mucosal system, in particular, are not merely idle bystanders in metabolic and physiological function. The gut appears to actively regulate the flow of amino acids from the diet to the body, apparently removing those amino acids that are necessary for the maintenance of its own integrity and physiological function.

Other articles in this supplement include references (59–68).

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