Review Article

Emerging aspects of dietary glutamate metabolism in the developing gut

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Glutamate is a major constituent of dietary protein and is also consumed in many prepared foods as a flavour additive in the form of monosodium glutamate (MSG). Evidence from human and animal studies indicates that glutamate is the major oxidative fuel for the gut and that dietary glutamate is extensively metabolized in first-pass by the intestinal enterocytes. Glutamate also is an important precursor for bioactive molecules, including glutathione, and functions as a key neurotransmitter. The central importance of glutamate as an oxidative fuel may have therapeutic potential for improving function of the infant gut, which exhibits a high rate of epithelial cell turnover. Our recent studies in infant pigs show that when MSG is fed at higher (4-fold) than normal dietary quantities, the majority (~70%) of glutamate molecule is either oxidized as energy or metabolized by the mucosa into other nonessential amino acids. Our results also showed that at high dietary intakes the rate of MSG absorption is higher when given via the intragastric compared to intraduodenal route. This intriguing finding implies that gastric glutamate transport may be physiologically significant and warrants further research into the role of MSG in gastric development and function during infancy.

Key Words: neonatal, neurotransmitter, intestinal oxidation, amino acids, monosodium glutamate

INTRODUCTION

The dicarboxylic, amino acid glutamate is a major oxidative fuel for the gut. In addition, glutamate is an important precursor for other biologically active molecules, including glutathione, proline and arginine, and also functions as a key neurotransmitter.[1] Several studies have shown that glutamate is extensively metabolized by the intestinal enterocytes. Seminal studies by Windmueller and Spaeth using an in situ perfused rat intestine established that only small fractions of luminally administered glutamate are absorbed into the mesenteric venous blood.[2,3] Subsequent studies in young pigs, preterm infants and adult humans have confirmed that dietary glutamate is extensively metabolized by the intestine and that oxidation to CO_2 is a major metabolic fate.[4-6] Our recent studies in young pigs also indicate that oxidation to CO_2 is a major metabolic fate of enteral glutamate even when the dietary intake fed is 3-4 fold higher than normal.[7]

There is compelling evidence that glutamate functions as a signalling molecule in the enteric nervous system and may modulate neuroendocrine reflexes in conjunction with the umami taste specifically,[8] and nutrient sensing in general.[9] Glutamate is the major excitatory neurotransmitter in the body and multiple glutamate receptors and transporters have been found in the gut and enteric nervous system (ENS).[10-12] Moreover, recent reports have shown that the two vesicular glutamate transporters (VGLUTs), VGLUT1 and VGLUT2, are present both in ENS and pancreatic tissue.[13] These studies imply that the gastric glutamate sensors exist and appear to play a role in gastrointestinal function. In addition to these findings, it remains unknown whether glutamate absorption and metabolism occurs in the stomach.

The central importance of glutamate as a major gut oxidative fuel and key enteric neurotransmitter may have therapeutic potential for improving neonatal gut function. The premature neonatal intestine exhibits a high rate of epithelial growth and cell turnover, but poorly developed gastro-duodenal function limits the ability to provide critically important enteral nutrition.[14,15] However, the use of glutamate as an enteral supplement to augment neonatal gut function should be considered in the context of previous reports of glutamate induced neurotoxicity.[16,17] Subsequent reviews have concluded that there is no evidence linking monosodium glutamate (MSG) to long term serious health problems in the general population. Moreover, the evidence of neurotoxicity in several experimental models only occurred with extremely high enteral and parenteral glutamate loads and thus MSG generally recognized as a safe as a food additive.[18]

The aim of the current review is to briefly examine the literature on intestinal glutamate metabolism in the developing gut and discuss the potential significance of recent findings from a functional, nutritional and clinical perspective.

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MAJOR GUT OXIDATIVE FUEL

In recent years, it has become increasingly evident that the gastrointestinal tissues derive a majority of its oxidative energy from the catabolism of amino acids, rather than glucose or fatty acids. The liver is a major site of amino acid metabolism and has been historically considered a major site of catabolism and oxidation. However, since the classic studies of Windmueller and Spaeth,[2,3] it has become apparent that the gut, particularly the intestine, is also a major site of catabolism of several amino acids, especially glutamate. Our studies in piglets confirmed these findings and demonstrated that ~90% of the dietary glutamate is metabolized by the gut and 50% of this is converted to CO_2 (Figure 1).[6,19] Other secondary products of gut glutamate metabolism in the pig studies were proline, alanine, arginine and lactate. Glutamate also serves as a key constitutive amino acid of glutathione, the major cellular antioxidant in the intestinal cells.[20] The importance of glutamate as a gut oxidative fuel has also been shown in studies in premature infants and adults.[4] These studies indicate that ~75-80% of the dietary glutamate intake is metabolized in first-pass by splanchnic tissues and that a large proportion >80% of this glutamate is oxidized to CO_2.

CAPACITY FOR GUT GLUTAMATE METABOLISM

We recently investigated the extent of gut glutamate metabolism in young pigs fed supraphysiological intakes of glutamate, given the concerns about dietary glutamate intake and possible neurotoxicity in early postnatal development.[7] We quantified the metabolic fate of dietary [^{13}C]-glutamate in young pigs when administered intraduodenally with a normal milk formula, control diet (~600 μmoL•kg^{-1}•h^{-1}) or diet supplemented with MSG up to 400% of the control glutamate intake. We found that the across the wide range of glutamate intakes (600-2100 μmoL•kg^{-1}•h^{-1}) the fractional percentage of glutamate absorption was not significantly different (13-17% dietary intake). However, the absolute rate of dietary glutamate absorption did increase significantly. When we compared the gut metabolism of [^{13}C]-glutamate, we found that oxidation to $^{13}CO_2$ was a major fate, yet was lower (33% vs. 49%) in pigs fed 350% vs 100% glutamate intake, respectively.

We also studied the metabolic fate of dietary [^{13}C]-glutamate in young pigs when administered the same control diet and supplemental glutamate intakes, but via the intragastric feeding route. We did this to simulate nasogastric feeding in infants. Similar to the intraduodenal feeding route, we found that oxidation to $^{13}CO_2$ was the major metabolic fate (35-42%) of intragastric [^{13}C]-glutamate fed. However, in contrast to intraduodenal feeding, the rate of intestinal glutamate absorption when given intragastrically was significantly higher 17% to 28% in pigs fed 100% vs. 300%, respectively (Figure 2).

We also measured the changes in the circulating arterial glutamate concentrations in pigs fed excessive dietary glutamate intakes. Our results showed that at the normal dietary intake, plasma arterial glutamate concentrations were not significantly increased by feeding, per se, when compared to the fasted condition (Figure 3). However, when fed 200% and 300% of the normal dietary intake, the circulating glutamate concentrations were significantly increased above the fasting level.

We compared the relationship between net intestinal glutamate absorption and dietary glutamate intake in pigs fed via either the intragastric or intraduodenal route (Figure 4). Our results suggest that the rate of dietary glutamate absorption is higher when feeding occurs via the intragastric route, but only when glutamate is fed in excess of the normal dietary intake.

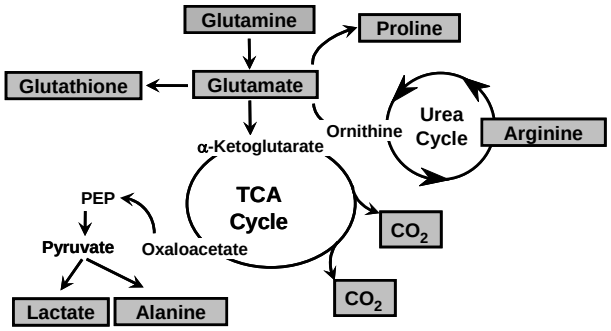

Figure 1. Pathways of glutamate metabolism in gastrointestinal tissues.

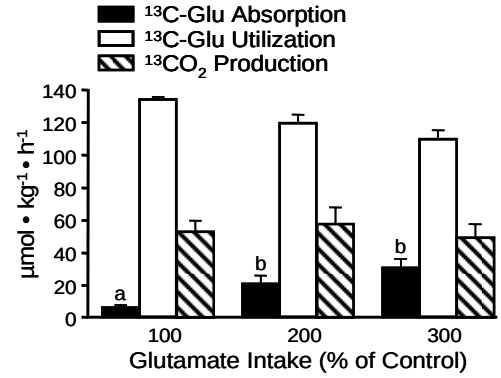

Figure 2. Rates of gut [^{13}C]glutamate tracer absorption, intestinal tracer utilization, and conversion to $^{13}CO_2$ in pigs fed 100, 200, or 300% of their enteral glutamate intake via the intragastric route. Bars represent means ± SEM, N=7-8 pigs/group. Means without a common superscript differ based on Tukey's multiple comparison test (p<0.05).[7]

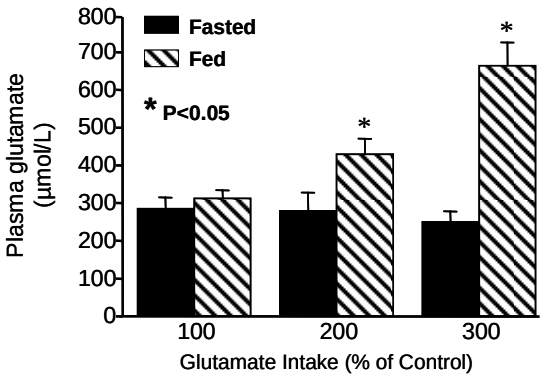

Figure 3. Fasted and fed arterial glutamate concentrations in young pigs given 100, 200, or 300% of their enteral glutamate intake via the intragastric route. * p<0.05 fed vs. the fasted group within a treatment group.[7]

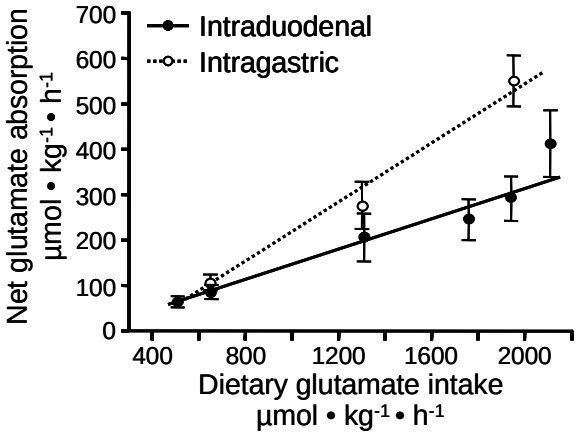

Figure 4. Relationship between net gut glutamate absorption and dietary glutamate intake in pigs fed intraduodenal or intragastric routes. Each point represents the mean ± SEM for N= 6-10 pigs[7].

METABOLIC CONSEQUENCES OF EXCESSIVE GUT GLUTAMATE METABOLISM

The findings from our most recent studies demonstrate that the gut capacity for metabolism of dietary glutamate is substantial, even when the intake is in excess of the normal level. Even when the dietary intake is increased three to four fold, a majority of the dietary glutamate intake is metabolized by the gut, either for generation of ATP or conversion into other amino acids. Apart from CO_2, most of the end-products of glutamate metabolism were predictably non-essential amino acids. For example, when the dietary glutamate intake was increased three fold, the net intestinal production of glutamine, aspartate, and ornithine increased significantly by 4.8, 4.0, and 2.7 fold, respectively. The intestinal absorption of other amino acids also tended (p<0.10) to increase in pigs fed excessive loads (300% level) of dietary glutamate, including proline, arginine, and branched-chain amino acids (BCAA). We would expect to see increased intestinal production of proline and arginine under excessive dietary glutamate intakes since these are by-products of glutamate metabolism via pyrroline -5-carboxylate. In contrast, the trend for increased BCAA production was surprising, yet this observation supports another recent study where we observed a 50% increase net intestinal leucine absorption in pigs fed supplemental alpha-ketoglutarate.[21] Importantly, this study showed that ~80% of dietary alpha-ketoglutarate is metabolized in first-pass by the gut and a third of this is oxidized to CO_2. Taken together, these findings suggest that under conditions of increased dietary availability of key gut oxidative substrates, namely glutamate and alpha-ketoglutarate, gut metabolism of BCAA is reduced or spared. This possibility is intriguing given the evidence in vivo and in vitro that BCAA are extensively oxidized by the gut to CO_2.[22-24] Moreover, glutamate and alpha-ketoglutarate are transamination partners in the reversible reaction catalysed by BCAA transaminase (BCAT). The relationship between dietary glutamate intake and essential amino acid oxidation in the gut merits further study.

GLUTAMATE AND GASTRIC FUNCTION

Our observation (see Figure 4) of increased gut glutamate absorption during intragastric vs. intraduodenal feeding suggests an active capacity for glutamate transport by the stomach mucosa. The direct evidence for amino acid transport and absorption across the gastric mucosa is limited, although several amino acid transporters are expressed in gastric epithelial cells including some involved in glutamate transport.[25,26] Gastric glutamate transport and absorption may be physiologically significant in dietary circumstances that involve feeding free amino acid based diets.

Glutamate has been shown to activate contractile action in the gastric fundus in several studies, possibly via cholinergic neurons.[27-29] A recent elegant study showed that intragastric glutamate infusion specifically stimulates afferent gastric vagal nerves, whereas all other amino acids had no effect. Moreover, the activation of vagal afferent activity was dose-dependent and effective well within the physiological range of normal dietary glutamate intakes. The mechanism whereby free luminal glutamate is sensed by the gastric mucosa warrants further study, but appears to involve 5-HT and NO production and release.[30] These studies suggest that neural sensing of gastric luminal glutamate may play a direct role in controlling digestion function.

CLINICAL APPLICATION IN PREMATURE INFANTS

Premature infants frequently present with significant gastroduodenal motor dysfunction, which is manifest clinically as feeding intolerance resulting from slow gastric emptying.[15] The consequence of feeding intolerance in premature infants is prolonged use of parenteral nutrition, delayed time to achieve full enteral feeding, increased morbidity and risk of infection, and delayed hospitalization. Despite this clinical problem, the neuroendocrine function of the developing gut is poorly understood. However, recent findings demonstrating that luminal glutamate activates gastric contractile activity may offer a therapeutic approach to stimulate gastric emptying and treat feeding intolerance in premature infants. A recent study in premature infants showed that acute feedings of supplemental glutamate at two and four fold higher than normal did not increase the circulating plasma glutamate concentration.[5,31] Thus, the available evidence indicates that supplemental glutamate is well tolerated and safe in premature infants.

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AUTHOR DISCLOSURES

Douglas G Burrin, Michael J Janeczko and Barbara Stoll, no conflicts of interest.

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