Glutamine promotes triglyceride absorption in a dose-dependent manner

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Received 21 August 2000; accepted in final form 14 August 2001

Schwimmer, Jeffrey B., Looi EE, Shuqin Zheng, and Patrick Tso. Glutamine promotes triglyceride absorption in a dose-dependent manner. Am J Physiol Gastrointest Liver Physiol 282: G317–G323, 2002.—Dietary proteins may play a role in lipid absorption. Whether amino acids are specifically involved is unknown. We hypothesized that enterally administered L-glutamine (L-Gln) given with a lipid meal increases triglyceride (TG) absorption in rats. Mesenteric lymph fistulae and gastroduodenal feeding tubes were placed in adult male Sprague-Dawley rats. The animals received an enteral bolus of Intralipid (5 ml) followed by enteral infusion of increasing concentrations of L-Gln in saline (0, 85, 170, or 340 mM) or equimolar concentrations of the inactive isomer D-Gln or an essential amino acid mixture without Gln. Lymph was collected continuously for 6 h and analyzed for TG content. Animals infused with 85 mM L-Gln had a 64% increase in total TG output vs. controls (P < 0.05) despite no difference in lymph flow rate. Total TG output for animals infused with 340 mM L-Gln declined by 43% vs. controls (P < 0.05). The effect of Gln in promoting lymphatic fat transport is specific to L-Gln and not shared by D-Gln or an equivalent amino acid mixture. L-Gln is capable of either promoting or impairing lymphatic TG transport in a dose-dependent manner.

enteral nutrition; intestinal lymph; lipid absorption

THE PROCESS OF LIPID ABSORPTION has largely been studied without accounting for the potential effects of other macronutrients. However, several studies (16) suggest a role for dietary protein in lipid absorption. Luminal proteins are capable of stabilizing triglyceride (TG) emulsions in vivo. Moreover, protein-stabilized emulsions are able to largely restore lymphatic TG output in bile duct-ligated rats. Fecal fat excretion is greater in infants fed a protein-free diet (15). Low birth weight infants fed a formula with an identical fat blend but different protein constituents have different fat absorption (2). Weber and Ehrlein (21) demonstrated that meal macronutrient composition alters the length of small intestine required for the complete absorption of fat.

L-Glutamine (L-Gln), the major source of fuel for enterocytes (8, 13), is one amino acid (AA) that may impact lipid absorption. In miniswine with severe burns, oral L-Gln was shown (23) to improve intestinal absorption of macronutrients including fats. The benefit of Gln when used in conjunction with growth hormone for patients with short bowel syndrome is controversial (3, 4, 18). In one study (18), however, half of the patients had improved fat balance.

Under normal conditions, the efficiency of fat absorption is ~96%. However, in diseased states such as burns, trauma, sepsis, and prematurity, lipid absorption is impaired; therefore, affected patients may benefit from a Gln supplement. We decided to test whether Gln affects intestinal lipid absorption. This information is important to gastrointestinal physiology and is clinically relevant.

The lymph fistula rat exploits the process of fat absorption to capture the lipid before it enters the circulation (1). Furthermore, lymph can be collected in a conscious animal without the confounding effect of anesthesia. Therefore, we chose the conscious lymph fistula rat model to test our hypothesis that enterally administered L-Gln given with a lipid meal enhances the total absorption of TG. We further hypothesize that this effect of L-Gln on fat absorption is dose specific.

MATERIALS AND METHODS

Animals

Adult male Sprague-Dawley rats weighing 250–275 g were purchased from Harlan Industries (Indianapolis, IN). All animals were quarantined for 1 wk to allow them to adjust to laboratory conditions. The rats had free access to standard chow and water. The room lighting was set for a 12:12-h light-dark cycle. The Institutional Animal Care and Use Committee of the University of Cincinnati (Cincinnati, OH) approved all procedures.

Operative Procedure and Recovery

The animals were fasted overnight but had free access to water. The rats were anesthetized with 2% halothane (Halocarbon Laboratories, River Edge, NJ) in an air-O2 mixture. The abdomen was prepared and shaved. A midline vertical incision was made from the xyphoid process to the suprapubic region. The intestines were retracted to the left onto sterile saline-soaked gauze. The lymph tubing [polyvinyl...

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GLUTAMINE AND TRIGLYCERIDE ABSORPTION

chloride (0.5 mm ID, 0.8 mm OD), Critchley Products, Silverwater BC, New South Wales, Australia] was flushed with a heparin-saline solution (1,000 U/ml). The duodenal feeding tube [silicone (1.02 mm ID, 2.16 mm OD), Helix Medical, Carpinteria, CA] was flushed with saline. The lymph cannula and the duodenal tubing were introduced into the peritoneal cavity through two punctures made with a 16-gauge needle. The mesenteric lymphatic duct was opened with ophthalmic iris scissors, and the tubing was placed into the lumen. The tube was secured with one drop of cyanoacrylate glue. The intestines were returned to the peritoneal cavity, and the stomach was retracted. A purse-string ligature was made in the fundus of the stomach. The stomach was punctured with a 16-gauge needle, and the catheter was introduced into the stomach and advanced 1 cm beyond the pylorus into the duodenum. The purse string was tied, fixing the tube in place. The abdominal musculature and skin were closed in two layers with 4-0 silk suture (Ethicon, Somerville, NJ). Postoperatively, a glucose-saline solution containing 145 mM NaCl, 4 mM KCl, and 280 mM glucose was infused into the duodenum at 3 ml/h. The animals were placed in restraint cages and allowed to recover overnight (18–22 h) in a temperature-regulated box maintained at 30°C.

Experimental Plan

To test the absorption of TG, we provided the total daily TG intake as a single lipid meal. We delivered an emulsified solution to the duodenum with Intralipid (ClinTec Nutrition, Deerfield, IL) as the TG source. A bolus of 5 ml of 20% Intralipid was chosen because this provides 1 g of TG, which is approximately the 24-h fat intake of an adult rat. The lipid bolus was then followed by a continuous intraduodenal infusion of a control (saline only) or experimental solution (saline + Gln). Experimental solutions contained 145 mM NaCl and increasing concentration of L-Gln (85, 170, or 340 mM). Continuous infusion with 145 mM NaCl and 0 mM L-Gln was chosen as a control solution to ensure adequate hydration and lymph flow. The Gln concentrations used were based on both clinical trials and saturability. We chose 85 mM L-Gln because it is in the range of solutions of supplemental Gln used in clinical trials. We also used two additional controls for 85 mM L-Gln. To test whether an effect was due to physiological activity, we used a solution with an equimolar concentration of the inactive isomer d-Gln. To assess whether an effect of 85 mM L-Gln is common to other AA, we mixed an equimolar concentration of an essential AA mixture without Gln (MEM essential AA 50× solution, BioWhittaker, Walkersville, MD) with water and NaCl to make a solution containing 145 mM NaCl and 85 mM of essential AA (85 mM AA). We chose 340 mM L-Gln because it is a maximally saturated solution. To assess whether the result with 340 mM L-Gln was physiological, we used an equimolar solution of d-Gln that also controlled for the high osmolarity of the saturated solution. Finally, we chose to test the intermediate concentration, 170 mM L-Gln.

Experimental Procedure

Lymph was collected into conical graduated centrifuge tubes on ice for 1 h to assess baseline (fasting) lymph flow and TG output. Animals with a baseline lymph flow rate <2 ml/h were excluded. The animals (n = 7/group) were then given a 5 ml duodenal bolus of Intralipid over 2 min. The lipid bolus was followed by a 3 ml/h continuous duodenal infusion of control or test solution for 6 h. Lymph was collected continuously on ice for 6 h and analyzed for TG content. TG concentrations were determined by the enzymatic method using a standard kit (procedure no. 334-UV, Sigma Diagnostics, St. Louis, MO).

Statistical Analysis

Statistical analysis was performed using statistical software (SAS Institute, Cary, NC). The overall differences in lymph flow rate over a 6-h period were evaluated with a repeated-measures ANCOVA with an α of 0.05. The repeated measure was time. We measured total lymphatic TG output continuously for 6 h after the ingestion of a lipid bolus. The overall differences in total TG output among the experimental and control groups were evaluated by a covariance test with an α of 0.05. Individual relationships between the groups for total TG output were evaluated using Tukey’s honest significant difference test. Individual relationships between the groups for hourly lymphatic TG output were evaluated via a priori nonorthogonal contrasts with a restricted Bonferroni α = 0.0028.

Chemicals

All chemicals and reagents, unless otherwise specified, were obtained from Sigma Chemical (St. Louis, MO) and were of analytical grade.

RESULTS

Lymph Flow

Increasing L-Gln concentrations. There was no significant difference in mean baseline lymph flow among the four L-Gln groups (0, 85, 170, and 340 mM L-Gln; Fig. 1). In all groups, the lymph flow rate increased in response to lipid feeding. With 0, 8, or 170 mM L-Gln, the lymph flow rate increased and peaked during the third hour. After the fourth hour, the rate returned to baseline. In contrast, the lymph flow rate in the group infused with 340 mM L-Gln increased in the first hour but declined thereafter. The lymph flow rates in the groups infused with 0 or 85 mM L-Gln were not different from each other. Animals infused with 170 mM L-Gln had a numerically greater volume of lymph flow over the 6 h, but this was not significantly different
from the 0 or 85 mM L-Gln groups. The lymph flow rate in the 170 mM L-Gln group was significantly different from the group infused with 340 mM L-Gln ($P < 0.05$). When the individual hourly lymph flow rates were compared, 340 mM L-Gln led to a significantly ($P < 0.0028$) lower lymph flow rate than did 0, 85, and 170 mM L-Gln for the third and fourth hour.

Controls and 85 mM L-Gln. The effects of 85 mM L-Gln were further evaluated by using the initial control, 0 mM L-Gln, and two additional controls, 85 mM D-Gln and 85 mM essential AA. Among these groups, baseline lymph flow was not significantly different (Fig. 2). The individual differences between the groups for each hour of the experiment were not significant, except for the 85 mM L-Gln and D-Gln groups during the fourth hour ($P = 0.001$).

Controls and 340 mM L-Gln. Using the initial control, 0 mM L-Gln, and an additional control, 340 mM D-Gln, the effects of 340 mM L-Gln were further evaluated. Fasting lymph flow was not significantly different between these groups (Fig. 3). Over time, however, a significant difference in the change of lymph flow rate between these groups ($P = 0.01$) was observed. When the individual relationships for lymph flow rate between these groups for each hour were evaluated, the lymph flow rate for the group infused with 340 mM L-Gln was significantly lower than that of the 0 mM L-Gln group during the third and fourth hour ($P < 0.0028$). Lymph flow in the group infused with 340 mM D-Gln was not significantly different from that of the 0 or 340 mM L-Gln group at any time point.

Lymphatic TG Output

Increasing L-Gln concentrations. The fasting lymphatic TG output was not significantly different among the four L-Gln groups (0, 85, 170, and 340 mM L-Gln; Fig. 4). After lipid feeding, there was a rapid rise in TG within the intestinal lymph in all groups. In the groups infused with 0 and 170 mM L-Gln, lymphatic TG content peaked during the third hour. Lymphatic TG content in the group infused with 85 mM L-Gln had a higher and longer increase that peaked during the fourth hour. The group infused with 340 mM L-Gln had an earlier and much lower peak during the second hour and a decline in TG output thereafter. There was a significant difference in the change of TG output over time between the four groups of rats studied (0, 85, 170, and 340 mM L-Gln) ($P < 0.05$). There was also a significant overall difference between the groups when levels were collapsed across time ($P < 0.0001$).

The hourly lymphatic TG output was summed to obtain total TG absorption (Fig. 5). The total TG absorption over the 6-h period for each group ($\mu$mol $\pm$ SE) in ascending order was $101 \pm 9$, $178 \pm 21$, $253 \pm 23$, and $292 \pm 17$ $\mu$mol for 340, 0, 170, and 85 mM L-Gln, respectively. The overall difference between the groups
was significant \( (P < 0.01) \). The group infused with 85 mM L-Gln and the group infused with 170 mM L-Gln were each significantly different from the 0 mM L-Gln group, but were not significantly different from each other. To test whether concentrations of L-Gln lower than 85 mM would also promote lymphatic TG transport we studied five additional animals receiving 42.5 mM L-Gln supplemented in the infusate. Lymphatic TG output in these animals was superimposable with the output observed in the animals infused with saline only (0 mM L-Gln; data not shown). We therefore concluded that the 42.5 mM dose of supplemented L-Gln had no effect on lymphatic TG output with the infused Intralipid. Thus it appears that promotion of lymphatic TG transport by 85 mM L-Gln is dose specific. Supporting this conclusion is the fact that the 340 mM L-Gln group had significantly lower TG output than the other three groups.

Controls and 85 mM L-Gln. Figure 6 shows the lymphatic TG output during the first 6 h after ingestion of a lipid meal. When individual relationships between the groups for hourly TG absorption were compared, the group infused with 85 mM L-Gln had a significantly higher TG output than the other three groups for the fourth, fifth, and sixth hours \( (P < 0.0028) \). The overall difference in total TG output between the group infused with 85 mM L-Gln and its three control groups was significant \( (P < 0.001) \) (Fig. 5). There was no significant difference in total TG output among the groups infused with 0 mM L-Gln, 85 mM D-Gln, or 85 mM AA (Fig. 5).

Controls and 340 mM L-Gln. The difference in fasting lymphatic TG output between groups at baseline was not significant (Fig. 7). After lipid feeding, the group infused with 340 mM D-Gln had a similar pattern as the group infused with 0 mM L-Gln, with a rapid rise in TG within the intestinal lymph that peaked during the third hour. The overall difference in total TG output between the group infused with 340

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**Fig. 5.** The total lymphatic TG output (in \( \mu \)mol) for experimental and control groups \( (n = 7/\text{group}) \) is shown over the 6-h period following a bolus of 1 g of TG. Values are means \( \pm \) SE.

**Fig. 6.** The mean lymphatic TG output is shown (in \( \mu \)mol) at baseline and hourly over 6 h following an intraduodenal bolus of 1 g of TG. After the bolus, each group \( (n = 7/\text{group}) \) received a continuous infusion of a solution containing no Gln or a solution of 85 mM L-Gln, the stereoisomer D-Gln, or AA. Values are means \( \pm \) SE.

**Fig. 7.** The mean lymphatic TG output is shown (in \( \mu \)mol) at baseline and hourly over 6 h following an intraduodenal bolus of 1 g of TG. After the bolus, each group \( (n = 7/\text{group}) \) received a continuous infusion of a solution containing no Gln or a solution of 340 mM L-Gln or the stereoisomer D-Gln. Values are means \( \pm \) SE.
mM L-Gln and the two control groups was significant (P < 0.001) (Fig. 7). The groups infused with 0 mM L-Gln and 340 mM D-Gln were not different from each other.

In a separate study, we compared the luminal recoveries of radioactive triolein incorporated in the 5 ml of Intralipid emulsion (i.e., 6 h after the introduction of Intralipid + saline, Intralipid + 85 mM L-Gln, or Intralipid + 340 mM L-Gln) (Table 1). As shown in Table 1, there was significant inhibition of the uptake of the radioactive fatty acids (FA) derived from the radioactive triolein when a high concentration of L-Gln was present in the intestinal lumen vs. a low concentration of L-Gln (85 mM) (P < 0.05) or saline (P < 0.05). There was no significant difference between 85 mM L-Gln and the saline controls.

We also determined the mucosal recoveries of the radioactive triolein incorporated in Intralipid at the end of the study. Mucosal lipids were extracted according to the method described by Folch et al. (7). As shown in Table 2, there was no significant difference in the amount of radioactive lipid recovered from the intestinal mucosa among the three groups of rats.

Additionally, we performed TLC analyses of the radioactive lipid in both the intestinal lumen and the intestinal mucosa. At the end of the infusion period, <10% of the radioactive triolein remained as TG in all three groups of rats and there was no difference between them. Therefore, L-Gln in different concentrations has no effect on the lipolysis of TG. Next, we analyzed the distribution of radioactive FA in the intestinal mucosa of the three groups of rats. Most of the radioactive FA (60–70%) was in the TG fraction in all three groups and there was no difference between them. Thus the presence of different concentrations of L-Gln in the intestinal lumen has no effect on the reesterification of absorbed monoglyceride and FA to form TG.

**DISCUSSION**

We chose to study Gln because of its diverse effects on the intestine. Using the intestinal lymph fistula rat model, we found that intraduodenal infusion of a solution containing 85 mM L-Gln led to a 64% increase in total lymphatic TG output after a lipid meal. This dramatic rise in TG output was not caused by a change in lymph flow, since the change in the lymph flow rate was comparable between the groups. We also observed a significant increase (42%) in TG output with 170 mM L-Gln, indicating that there is a range of L-Gln that promotes TG output. Because 42.5 mM L-Gln failed to stimulate lymphatic TG transport, we can infer that 85 mM is probably the optimal dose for maximum stimulation of lymphatic TG transport. This observation supports our first hypothesis that the absorption of L-Gln promotes intestinal absorption of lipid into lymph.

Next, we addressed the question of whether the enhancement of lymphatic TG transport is a specific action of L-Gln. Interestingly, infusion of an 85 mM solution of the stereoisomer D-Gln did not change the lymph flow or the TG output compared with 0 mM L-Gln. Therefore, the effect of 85 mM L-Gln is due to a cellular action of L-Gln and not to only the physical presence of Gln. To further test this specific action of L-Gln on intestinal lipid absorption into lymph, we infused 85 mM AA. As expected, TG output was significantly greater in rats infused with 85 mM L-Gln than in those infused with 85 mM AA (P < 0.001). The AA mixture did result in TG output that was 30% higher than with 0 mM L-Gln; this difference, however, did not reach significance. Therefore, the effect of 85 mM L-Gln on TG output by enterocytes is specific to L-Gln and cannot be generalized to mixed AA. These experiments do not exclude, however, the possibility that other AA may play a similar role in enhancing TG absorption. Actually, these data (30% stimulation of lymphatic TG transport) suggest that there are other AA that stimulate lymphatic TG transport.

In contrast to the intraduodenal infusion of 85 or 170 mM L-Gln, intraduodenal infusion of 340 mM L-Gln led to a 43% decrease in TG output compared with the Gln-free control. This data implies that higher doses of intraduodenally infused L-Gln actually decrease rather than increase intestinal lipid absorption into lymph. Analysis of radioactive triolein given with the Intralipid indicated that more radioactive FA remained in the intestinal lumen of animals infused with 340 mM L-Gln than in animals infused with either 85 mM L-Gln or saline. Although not conclusive, decreased uptake of FA by the small intestine in the presence of a high concentration of L-Gln was partially responsible for the decreased transport of lipid into lymph. Given the high osmolarity of the solution and the decrease in lymph flow, it is possible that these findings were a result of the hypertonicity of the solution. However, no change in TG output compared with 0 mM L-Gln was observed when using a solution with the same osmolarity containing 340 mM D-Gln. If the decreased TG output was due to an osmotic effect, then 340 mM D-Gln

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<th>Table 2. Mucosal recoveries of radioactive triolein</th>
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<tr>
<td>Intralipid + saline</td>
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<td>Intralipid + 85 mM L-Gln</td>
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<td>Intralipid + 340 mM L-Gln</td>
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Values are means ± SE given as %dose incorporated in Intralipid; n = 4/group.

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<td>Intralipid + saline</td>
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<td>Intralipid + 85 mM L-Gln</td>
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Values are means ± SE given as %dose incorporated in Intralipid; n = 4/group. L-Gln, L-glutamine. *P < 0.05 vs. saline and 85 mM L-Gln groups.
should have demonstrated the same effect. Therefore, the decline in TG output cannot be attributed to hypertonicity but instead is probably caused by the high concentration of l-Gln.

We also examined the mucosal radioactive FA recovery of animals given Intralipid incorporated with radioactive triolein (Table 2). We found no difference in the amounts of radioactive FA between the three groups (Intralipid + saline, Intralipid + 85 mM l-Gln, and Intralipid + 340 mM l-Gln). Additionally, despite the high concentration of l-Gln in the lumen (340 mM l-Gln), reesterification of absorbed 2-monoglyceride and FA to form TG was not affected, as shown by the similar distribution of radioactive FA in the various lipid fractions in the mucosa of the three groups of rats. The effect of a high dose of l-Gln on lipid absorption is physiologically relevant, but currently we cannot fully explain the mechanisms by which lymphatic TG transport is decreased.

Apolipoprotein B (apo B) is essential for chylomicon (CM) formation and thus TG output (6). AA are needed to form apolipoproteins, and as such, the enhancement of observed TG output may be an effect of high AA concentrations. Furthermore, supplemental Gln has been shown to increase total protein synthesis in jejunal enteroctyes (10). However, it seems unlikely that the effect of Gln on intestinal lipid absorption is mediated through increased apo B secretion for the following three reasons. First, the equimolar AA did not have a significant effect on TG output. Second, TG flux is not believed to stimulate intestinal apo B synthesis. Instead, enterocytes transport absorbed dietary lipid by increasing the size of CM particles and not by increasing their number (9). Third, perhaps the effect of Gln is achieved by supplying more energy to the process of CM packaging, since energy is required for this process and Gln has been demonstrated (22) to be the preferred energy source by the enterocytes.

In conclusion, l-Gln promotes TG absorption in a dose-dependent manner, and its effect is specific compared with an AA mixture. Whether other single AA show similar properties is unknown. The mechanism by which l-Gln effects TG absorption is unclear. A likely target is the process of CM packaging and export, which will require further investigation to be fully understood.

There are several potential clinically relevant aspects to the effect of Gln on TG absorption. Throughout the body, Gln consumption is highest in the jejunum and helps to maintain the integrity of the intestinal mucosa (19, 20). Supplemental Gln has also been shown (5, 12, 14) to have many beneficial effects. Gln stimulates sodium and water absorption (11, 17). In very low birth weight infants, Gln-supplemented formula improved the tolerance of enteral feeding (5, 14). Adult patients who were critically ill had a decreased need for parenteral supplementation when their feedings were supplemented with Gln (12). The data presented in this study raise the possibility of dose-specific l-Gln playing a therapeutic role in fat malabsorption.

We thank Drs. W. Balistreri, M. Cohen, and J. Heubi for the thoughtful manuscript reviews. This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grants DK-54504, DK-56910, and DK-56863. J. Schwimmer was the recipient of National Research Service Award DK-07727.

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AJP-Gastrointest Liver Physiol • VOL 282 • FEBRUARY 2002 • www.ajpgi.org


