Glutamine Metabolism of Intestine Grafts: Influence of Mucosal Injury by Prolonged Preservation and Transplantation

A. Nemoto, A. Krajack, T. Suzuki, I. Takeyoshi, N. Hamada, M. Nomoto, S. Zhang, Y. Zhu, T.E. Starzl, and S. Todo

GLUTAMINE is the principal respiratory fuel of the enterocyte.[1] It is an essential precursor for purine and primidine synthesis, and is required for DNA biosynthesis and cell division in the crypt cells of the gut mucosa.[2] While it has been shown that in various stress situations, such as prolonged fasting[3] and operative stress,[4] glutamine consumption by the intestine is significantly increased, no detailed studies have shown the effect of severe preservation and reperfusion injury on gut glutamine metabolism after intestinal transplantation. The purpose of this study is to examine enteric and extraenteric glutamine metabolism in the canine intestine after 24 hours preservation and intestinal autotransplantation, and to assess whether glutamine-enriched total parenteral nutrition is beneficial for intestinal recovery from severe preservation and reperfusion injury.

MATERIALS AND METHODS

Thirty-five adult mongrel dogs of either sex weighing 17 to 25 kg were used for this study. Animals were divided into seven groups of five animals based on preservation time and day of killing. Grafts were either transplanted immediately (group I) or transplanted after 24 hours of preservation in lactated Ringer's solution (group P). Animals were killed on 3, 7, and 14 days postoperatively. Untransplanted animals (n = 5) were used as controls. Glutamine metabolism in the intestine, liver, skeletal muscle, and kidney was studied. Blood samples were taken from the femoral artery, and portal, hepatic, femoral, and renal veins before and during a 60-minute intravenous (IV) infusion of glutamine (0.1 g/kg). Glutamine and ammonia concentrations were determined using high-performance liquid chromatography (HPLC) and the glutamine dehydrogenase reaction, respectively. Superior mesentric, hepatic, femoral, and renal arteries and portal vein blood flows were determined before and during glutamine infusion using ultrasonic flow probes (Transonic, Ithaca, NY). Plasma flow was calculated using blood flow and hematocrit values. These measurements were performed on postoperative days 3, 7, and 14.

RESULTS

Net glutamine balance in the intestine, liver, skeletal muscle, and kidney is shown in Table 1. Before glutamine infusion, gut glutamine uptake was significantly elevated in group P 3 days after transplantation. Glutamine uptake by the preserved graft 3 days after transplantation correlated with an enhanced output of ammonia at the same time point, but the increase in the ammonia level was not statistically significant. The demand for glutamine by the preserved graft 3 days after transplantation was significantly higher than all other groups throughout the glutamine infusion. Ammonia output during glutamine infusion was significantly enhanced in response to the increased utilization of glutamine by the enterocytes of the preserved grafts 3 days after transplantation. While the liver normally takes in glutamine and ammonia to make urea through the urea cycle, the liver of the preserved grafts 3 days after transplantation becomes a net producer of glutamine in response to the increased glutamine demand by the intestine. To

From the Pittsburgh Transplantation Institute, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address reprint requests to Satoru Todo, MD, Pittsburgh Transplantation Institute, 5C Falk Clinic, 3601 Fifth Avenue, Pittsburgh, PA 15213.

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Table 1. Net Glutamine Balance

		Immediate			Preservation		
Postoperative Day	Control	3	7	14	3	7	14
Intestine							
Before	0.893 ± 0.196	1.047 ± 0.160	0.985 ± 0.130	0.993 ± 0.174	1.473 ± 0.196*	1.106 ± 0.101	0.991 ± 0.236
After	1.877 ± 0.241	1.987 ± 0.249	1.962 ± 0.137	1.942 ± 0.241	2.680 ± 0.350*	2.128 ± 0.209	1.901 ± 0.274
Liver							
Before	0.615 ± 0.166	0.549 ± 0.145	0.608 ± 0.140	0.616 ± 0.133	−0.119 ± 0.101†	0.469 ± 0.112	0.606 ± 0.132
Skeletal muscle							
Before	−0.334 ± 0.055	−0.346 ± 0.064	−0.345 ± 0.062	−0.343 ± 0.048	−0.564 ± 0.091*	−0.412 ± 0.078	−0.351 ± 0.065
Kidney							
Before	0.088 ± 0.015	0.094 ± 0.018	0.094 ± 0.012	0.089 ± 0.016	0.104 ± 0.016	0.098 ± 0.016	0.090 ± 0.017

Note: Values are means ± SEM. Net glutamine balances are in μmol/min/kg body weight. Before, before glutamine infusion; after, 60 min after starting glutamine infusion.

*$P < .05$: vs control, I3, I7, I14, and P14, analysis of variance.

†$P < .05$: vs control, I3, I7, I14, P7, and P14.

produce the excess glutamine, ammonia uptake by the liver is significantly augmented. Skeletal muscle, a major supplier of glutamine, significantly increases the supply of glutamine to the preserved graft 3 days after transplantation. As with the liver, ammonia uptake by the skeletal muscle was significantly augmented to supply the excess glutamine. There were no changes in glutamine uptake and ammonia output by the kidney.

SUMMARY

The demand for glutamine increased only in the preserved intestine in the early postoperative period (3 days after transplantation). Glutamine demand of the preserved grafts returned to control and immediate levels 7 and 14 days after transplantation. Three days after intestinal transplantation, when the intestinal mucosa was actively regenerating, the demand for glutamine was markedly enhanced. The enhanced demand for glutamine was met by increased output of glutamine by the liver and skeletal muscle. Glutamine uptake by the intestinal graft was enhanced by a brief infusion of glutamine. Thus, we believe exogenous glutamine supplementation may be beneficial for the recovery of intestinal grafts with severe mucosal injury.

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