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Metabolism Clinical and Experimental 60 (2011) 867–873
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Continuous low-dose fructose infusion does not reverse glucagon-mediated decrease in hepatic glucose utilization

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Received 17 December 2009; accepted 18 August 2010

Abstract

An adaptation to continuous total parenteral nutrition (TPN; 75% of nonprotein calories as glucose) is the liver becomes a major consumer of glucose with lactate release as a by-product. The liver is able to further increase liver glucose uptake when a small dose of fructose is acutely infused via the portal system. Glucagon, commonly elevated during inflammatory stress, is a potent inhibitor of glucose uptake by the liver during TPN. The aim was to determine if continuous fructose infusion could overcome the glucagon-mediated decrease in hepatic glucose uptake. Studies were performed in conscious, insulin-treated, chronically catheterized, pancreatectomized dogs that adapted to TPN for 33 hours. They were then assigned to 1 of 4 groups: TPN (C), TPN + fructose (4.4 μmol kg^{-1} min^{-1}; F), TPN + glucagon (0.2 pmol kg^{-1} min^{-1}; GGN), or TPN + fructose and glucagon (F + GGN) for an additional 63 hours (33-96 hours). Insulin, fructose, and glucagon were infused into the portal vein. During that period, all animals received a fixed insulin infusion of 0.4 mU·kg^{-1}·min^{-1} (33-96 hours); and the glucose infusion rates were adjusted to maintain euglycemia (6.6 mmol/L). Continuous fructose infusion was unable to further enhance net hepatic glucose uptake (in micromoles per kilogram per minute) (31.1 ± 2.8 vs 36.1 ± 5.0; C vs F), nor was it able to overcome glucagon-mediated decrease in net hepatic glucose uptake (10.0 ± 4.4 vs 12.2 ± 3.9; GGN vs F + GGN). In summary, continuous fructose infusion cannot augment liver glucose uptake during TPN; nor can it overcome the inhibitory effects of glucagon.

1. Introduction

Individuals in stressed states such as sepsis, trauma, and burns often are unable to receive nutritional support via the enteral route; total parenteral nutrition (TPN) is an important intervention required to meet caloric needs [1-3]. Unfortunately, hyperglycemia is a common complication. It is controversial if tight glucose control improved outcomes including mortality [1,2,4,5].

The liver plays a central in the regulation of glucose homeostasis especially during continuous TPN; TPN augments its capacity to remove glucose and metabolize it to lactate [6,7]. This response, although present, is attenuated in the presence of an underlying stress such as infection [8]. Hospitalized patients receiving carbohydrate-rich TPN experience hyperglycemia [9]. The inability of the liver to switch from a glucose-producing organ to a glucose-consuming organ in response to TPN contributes to the hyperglycemia [10]. Thus, approaches that can sustain or augment hepatic glucose utilization may limit stress-induced hyperglycemia in nutritionally supported patients.

Fructose is a potent stimulator of liver glucose uptake. It can augment phosphorylation, glycogen synthetic, and glycolytic capacity of the liver by the activation of glucokinase (GK) and 6-phosphofructo-1-kinase. Fructose-1-phosphate generated by hepatic metabolism of fructose activates GK by inhibiting the binding of GK to GK regulatory protein. The binding of GK to 6-phosphofructo-2-kinase (PFK-2)/fructose-2,6-bisphosphatase facilitates the activation of 6-phosphofructo-1-kinase [11,12]. Whereas

Author contributions: Drs Johnson, Chen, and McGuinness helped in the study design; study execution; data collection, analysis, and interpretation; and manuscript writing. Phil Williams, Tammy Santomango, and D Brooks Lacy helped conduct the study and collect data.

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✠ Died July 18, 2008.

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doi:10.1016/j.metabol.2010.08.006

high-fructose diets can induce insulin resistance [13,14], when small amounts of fructose (7.5 g) are added to a 75-g oral glucose load, glucose tolerance is improved [15]. Interestingly, this percentage is similar to the fructose consumption (10%-15% of daily carbohydrate intake) in the American diet [16]. Fructose has been used as a nonglucose source for carbohydrate in nutritionally supported patients [17]. Infusions of small amounts of fructose in vivo in the fasted state enhanced net hepatic glucose uptake (NHGU) in a dose-dependent manner [18]. This increase does not persist when fructose is continuously infused possibly because of compensatory decreases in insulin secretion. Thus, continuous fructose infusion may in the absence of pancreatic adaptations augment liver glucose uptake in the TPN-adapted animal.

Glucagon is a potent inhibitor of the TPN-mediated increase in NHGU [19]. It is increased during infection and contributes to the infection-induced impairment in NHGU and to the associated hyperglycemia [20]. Glucagon is an inhibitor of hepatic glycolysis and of both GK and 6-phosphofructo-1-kinase. The aim was to assess whether continuous infusion of fructose can augment liver glucose uptake and reverse the glucagon-mediated decrease in NHGU and hepatic glycolysis in a setting where pancreatic compensation cannot occur. The chronically catheterized conscious dog model in which the pancreas is removed and insulin is replaced allowed us to examine the continuous interaction of fructose and glucagon in a setting of a fixed insulin and glucose environment during TPN.

2. Methods

2.1. Animal preparation

Male and female nonpregnant mongrel dogs were fed standard Kal-Kan meat (Vernon, CA) and Purina Lab Canine Diet (Purina Mills, St Louis, MO) once daily and had free access to water. Dogs were housed in a facility that met Association for Assessment and Accreditation of Laboratory Animal Care International guidelines. All protocols were approved by the Vanderbilt University Medical Center Animal Care Committee. Before surgery and before the initiation of continuous insulin administration and parenteral nutritional support, animals were determined to be healthy if they had a good appetite (ie, consumed at least 75% of the daily ration), normal stools, a hematocrit greater than 35%, and a leukocyte count less than 18 000/mm^3. Animals with symptoms of liver disease or infection or with inconsistent eating habits were excluded from the study or data analysis.

2.2. Experiment preparation

A laparotomy was performed using sterile techniques with general anesthesia. During the laparotomy, the pancreas was removed; and blood sampling catheters were placed in the portal and left common hepatic veins. Infusion catheters were placed in the splenic vein for insulin and/or glucagon administration and in the inferior vena cava (IVC) for delivery of nutritional support. Flow probes (Transonic Systems, Ithaca, NY) were placed in the left common iliac vein with the tip positioned distal to the anastomosis with the IVC and in the abdominal aorta via the right external iliac artery [19,21].

After removal of the pancreas, dogs were treated with subcutaneous injections of regular (~11 U/d; Eli Lilly, Indianapolis, IN) and NPH (~18 U/d; intermediate-acting insulin) insulin daily. The doses were adjusted to maintain near normoglycemia (glucose concentration was checked twice daily). The insulin injections were stopped when TPN was initiated. A variable intraportal insulin infusion was then given to maintain normoglycemia. Pancrease MT10 (Ortho-McNeil Pharmaceuticals, Raritan, NJ) was added to the diet to facilitate digestion after the pancreas was removed.

2.3. Nutritional support (TPN)

Free catheter ends were exteriorized from the subcutaneous pocket under local anesthesia (2% Lidocaine; Abbott, North Chicago, IL) after allowing at least 14 days for recovery from surgery. Total parenteral nutrition was infused into one of the IVC catheters with an ambulatory infusion pump (Dakmed, Buffalo, NY). Insulin or glucagon was infused into the catheter in the splenic vein by means of an infusion pump (Walkmed-350; Mckinley, Lakewood, CO). All dogs wore a jacket (Alice King Chatham, Los Angeles, CA) with 2 large pockets to hold the TPN-containing bag and pumps. Once initiated, TPN was the sole exogenous caloric source for 4 days. The TPN was designed to be isocaloric based on predicted resting energy expenditure. In addition to saline, potassium, phosphates, and a multivitamin supplement, the TPN contained glucose (50% dextrose; provided 75% of nonprotein calories), 20% Intralipid (Baxter Healthcare, Deerfield, IL; provided 25% of the nonprotein calories), and Travasol (Baxter Healthcare, Deerfield, IL) to supply basal nitrogen requirements.

2.4. Experimental design

All dogs received continuous TPN for 4 days. The bag was changed once daily. The animals were completely adapted to TPN after 48 hours, and liver glucose uptake remained constant thereafter. A variable intraportal infusion of insulin was given to maintain euglycemia (~6.6 mmol/L; 120 mg/dL) for the first 48 hours and was thereafter held constant at 0.4 mU kg^{-1} min^{-1} for the duration of the study. Animals were then assigned to 1 of 4 groups (n = 6-8 per group)—control (C), fructose infusion (4.4 μmol kg^{-1} min^{-1}; F), basal infusion of glucagon (0.2 pmol kg^{-1} min^{-1}; GGN), or combined glucagon and fructose infusion (F + GGN)—and were infused for an additional 48 hours. In a separate group of studies (n = 5), fructose, xylitol (4.2-5.2 μmol kg^{-1} min^{-1}), and glucagon were infused. These latter studies were discontinued because of liver complications.

Insulin, fructose, xylitol, and glucagon were infused into the portal vein.

2.5. Experimental protocol

After 48 hours of receiving the assigned infusions, hepatic and nonhepatic metabolism was assessed. On the morning of the study, all free ends of the catheters and flow probes (Transonic Systems) were exteriorized under local anesthesia. For the duration of the study, the dog was placed in a Pavlov harness. A primed (10 μCi) continuous (0.1 μCi/min) infusion of [3-^{3}H] glucose was infused into the IVC for the duration of the study. After a 120-minute equilibration period, blood samples were taken every 30 minutes between 120 and 240 minutes. Blood samples were taken from the artery, portal vein, hepatic vein, and iliac vein. Throughout the study period, all nutritional support and hormone infusion were continued. At the conclusion of the study period, animals were killed with a lethal dose of pentobarbital sodium. Tissue samples were then taken from each lobe of liver along with a skeletal muscle sample. All tissue samples were immediately frozen with a Wollenberger clamp precooled in liquid nitrogen and stored at −70°C.

2.6. Calculations

Net hepatic substrate uptake was calculated using the formula $[(F_a \times A) + (F_p \times P) - H] \times$ HBF, where A, P, and H represent blood substrate concentrations in the femoral artery, portal vein, and hepatic veins, respectively. F_a and F_p are the fractional contributions of the hepatic artery and the portal veins, respectively, to the total hepatic blood flow (HBF). Blood lactate, alanine, glycerol, and β-hydroxybutyrate and liver glycogen content and GK activity were assessed as described previously [22-24]. Hepatic glucose production was calculated as the difference between the unidirectional hepatic glucose uptake (HGU) and NHGU, where HGU is the ratio of hepatic [^{3}H] glucose uptake and the corresponding [^{3}H] glucose specific activity. Net nonhepatic glucose uptake was calculated as the difference between exogenous glucose infusion rate and NHGU. Hepatic glycogen cycling was calculated as the total tracer incorporation of [^{3}H] glucose into liver glycogen (disintegrations per minute) divided by the product of the plasma glucose specific activity (disintegrations per minute per milligram), body weight, and time.

2.7. Statistics

All data were expressed as means ± SEM. Statistical analysis was performed using mixed effects model for repeated measures. Toeplitz covariance was used in the model. Pairwise comparisons were not made unless the overall model for each variable tested met the significance level of $P < .05$. All data are reported as an average of 5 points during the sampling period. SPSS (Chicago, IL) version 17.0 was used for all statistical analysis.

3. Results

3.1. General characteristics and hormones

Body weight, liver weight, and blood flow (hepatic artery, portal vein, and iliac artery) were measured in C, F, GGN, and F + GGN groups and are shown in Table 1. Blood flow rates were not different between groups. Arterial plasma insulin and cortisol concentrations were similar across groups and did not change significantly over time (Table 1). The glucagon concentration was increased in the glucagon-infused groups.

3.2. Hepatic glucose metabolism

Arterial plasma glucose concentration (Fig. 1) was clamped at similar concentrations in all 4 groups. Net hepatic glucose uptake was not further increased by continuous fructose infusion (C vs F). Continuous glucagon infusion impaired NHGU, and this decrease was not reversed by continuous fructose infusion (Fig. 1).

Although hepatic glucose production did not statistically differ among the 4 groups, unidirectional hepatic uptake (HGU) was significantly different among C and F compared with F + GGN ($P < .001$) (Table 2). Fructose had no effect on HGU or NHGU in the presence of glucagon when compared with glucagon alone (Fig. 1). Glucagon infusion decreased hepatic glycogen content and liver mass. Fructose enhanced

Table 1
Body and liver weights, basal hemodynamics, and hormone concentration in chronically catheterized conscious dogs receiving TPN (C), TPN and fructose (F), TPN and glucagon (GGN), or TPN and both F and GGN (F + GGN)

	C	F	GGN	F + GGN
Body weight, kg	21 ± 2.4	21 ± 0.8	21 ± 1.3	21 ± 2.4
Liver weight, g	1037 ± 122	1112 ± 112	794 ± 260	980 ± 213
Hepatic arterial blood flow, mL kg^{-1} min^{-1}	5 ± 1	6 ± 1	6 ± 1	5 ± 1
Portal vein blood flow, mL kg^{-1} min^{-1}	24 ± 3	21 ± 2	19 ± 2	22 ± 2
Iliac artery blood flow, mL kg^{-1} min^{-1}	6.4 ± 0.5	5.6 ± 0.8	7.2 ± 1.2	6.0 ± 1.0
Arterial plasma insulin, μU/mL	9.8 ± 2.1	11.1 ± 1.8	9.4 ± 1.4	7.1 ± 0.7
Arterial plasma cortisol, μg/dL	3.4 ± 0.5	3.5 ± 0.3	3.6 ± 0.4	3.9 ± 0.3
Arterial plasma glucagon, pg/mL	24 ± 5	21 ± 3	39 ± 3*	33 ± 4*

Data are expressed as mean ± SEM.
* $P < .05$ vs C.

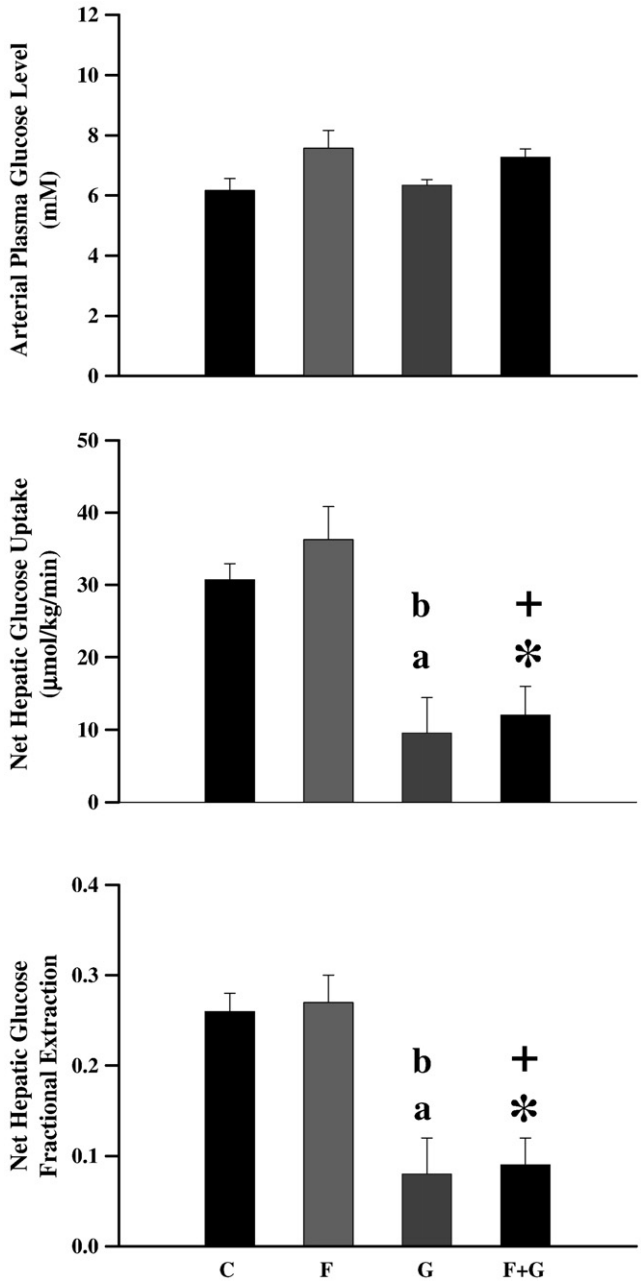

Fig. 1. Arterial plasma glucose concentration, NHGU, and net hepatic glucose fractional extraction in chronically catheterized conscious dogs receiving TPN (C), TPN and fructose (F), TPN and glucagon (GGN), or TPN and both F and GGN (F + GGN). Net hepatic glucose uptake: F + GGN vs C, *$P < .005$; F + GGN vs F, $^{+}P < .005$; G vs C, $^{a}P < .005$; GGN vs F, $^{b}P < .005$. Glucose fractional extraction: F + GGN vs C, *$P < .005$; F + GGN vs F, $^{+}P < .005$; GGN vs C, $^{a}P < .005$; GGN vs F, $^{b}P < .005$. Data are expressed as mean ± SEM.

glycogen deposition, but was unable to overcome the effects of glucagon when given in combination (Table 2). Hepatic glycogen cycling was increased by fructose infusion (3.8 ± 0.5 vs 8.3 ± 0.5 mg kg^{-1} min^{-1}; C vs F; $P < .05$), and infusion of glucagon decreased hepatic glycogen cycling and attenuated the fructose-mediated increase in hepatic glycogen cycling (0.5 ± 0.5 vs 1.6 ± 0.5 μmol kg^{-1} min^{-1}; GGN vs F + GGN).

Table 2
Tracer determined hepatic glucose flux and hepatic glycogen content and GK activity in chronically catheterized conscious dogs receiving TPN (C), TPN and fructose (F), TPN and glucagon (GGN), or TPN and both F and GGN (F + GGN)

	C	F	GGN	F + GGN
Unidirectional hepatic glucose uptake, μmol kg^{-1} min^{-1}	32.2 ± 2.8	43.9 ± 3.9	17.8 ± 3.9	16.1 ± 3.3*
Hepatic glucose production, μmol kg^{-1} min^{-1}	2.2 ± 1.7	7.2 ± 3.9	7.8 ± 3.3	4.4 ± 1.1
Glycogen, μmol/g liver	589 ± 44	722 ± 33	344 ± 67	539 ± 72
GK, μU/mg protein	11.5 ± 1.5	6.4 ± 0.9	9.7 ± 1.1	17.6 ± 5.3

Data are expressed as mean ± SEM.
* C vs F + GGN, F vs F + GGN; $P < .001$.

3.3. Metabolic substrate kinetics

Arterial lactate levels did not differ among the 4 groups (Table 3). Net hepatic lactate output in the control and fructose alone groups was similar. However, glucagon decreased net hepatic lactate release by up to 40% in the glucagon groups compared with control and fructose-alone groups. Whereas β-OH-butyrate and glycerol kinetics were not altered by glucagon or fructose, nonesterified fatty acid (NEFA) levels and net hepatic uptake of NEFAs increased in the glucagon-treated animals. Glucagon infusion increased net hepatic fractional extraction of alanine and decreased arterial concentration of alanine. Interestingly, continuous fructose infusion attenuated the glucagon-mediated increase in net hepatic alanine uptake and fractional extraction.

3.4. Nonhepatic glucose metabolism

Nonhepatic glucose uptake tended to increase with fructose alone, but decreased in the presence of glucagon (21.2 ± 2.1, 24.6 ± 3.6, 15.9 ± 3.7, and 20.5 ± 4.0 μmol kg^{-1} min^{-1}; C, F, GGN, and F + GGN; $P < .05$ C vs GGN). This decrease was absent when fructose and glucagon were combined.

4. Discussion

Hyperglycemia is a major problem in stressed patients receiving TPN. The objective was to determine if the addition of small quantities of fructose known to acutely augment hepatic glucose phosphorylation capacity to the TPN infusate could ameliorate the glucagon-mediated decrease in hepatic glucose disposal. Using the chronically catheterized, pancreatectomized, conscious dog model that was insulin treated, we examined the chronic interaction of glucagon and fructose in modulating liver glucose uptake in

Table 3
Arterial substrate concentrations, net hepatic substrate uptake, and net hepatic substrate fractional extraction in chronically catheterized conscious dogs receiving TPN (C), TPN and fructose (F), TPN and glucagon (GGN), or TPN and both F and GGN (F + GGN)

	C	F	GGN	F + GGN
Lactate concentration	1199 ± 163	1725 ± 295	1398 ± 411	1651 ± 333
Lactate uptake	−38 ± 2	−37 ± 4	−20 ± 7*	−16 ± 4*
Alanine concentration	915 ± 121	1040 ± 182†	545 ± 101*	675 ± 93
Alanine uptake	0.90 ± 0.57	1.19 ± 0.81	2.21 ± 0.25*	1.62 ± 0.33
Alanine FE	0.03 ± 0.02	0.05 ± 0.03†	0.20 ± 0.07*	0.09 ± 0.01*
Glycerol concentration	62 ± 4	52 ± 7	61 ± 11	61 ± 8
Glycerol uptake	1.02 ± 0.10	1.03 ± 0.15	1.01 ± 0.24	1.16 ± 0.19
Glycerol FE	0.61 ± 0.05	0.67 ± 0.02	0.70 ± 0.04	0.70 ± 0.03
β-OH-butyrate concentration	25 ± 2	26 ± 2	26 ± 3	22 ± 5
β-OH-butyrate uptake	−0.27 ± 0.08	−0.20 ± 0.1	−0.51 ± 0.05	−0.40 ± 0.10
NEFA concentration	220 ± 34	202 ± 15†	396 ± 35	294 ± 46
NEFA uptake	0.14 ± 0.19	0.37 ± 0.31	1.39 ± 0.56*	0.98 ± 0.31*
NEFA FE	0.03 ± 0.06	0.06 ± 0.05†	0.20 ± 0.12*	0.16 ± 0.02*

Data are expressed as mean ± SEM. Concentrations are in micromoles per liter; uptake rates are in micromoles per kilogram per minute. FE indicates fractional hepatic extraction.

* $P < .05$ vs C.

† $P < .05$ vs GGN.

the absence of compensatory changes in insulin secretion. Continuous infusion of TPN augmented NHGU, and very low doses of glucagon impaired this response [6,19]. The infusion of fructose was unable to attenuate this decrease. Thus, using a low dose of fructose to augment hepatic glucose phosphorylation capacity alone may not be an effective target to improve hepatic glucose utilization in stressed patients receiving TPN.

Continuous fructose infusion did not further enhance NHGU in TPN-adapted animals even when pancreatic compensation was prevented. In the complete absence of insulin, fructose at low concentrations translocates and activates GK [12,25]. Having complete control of the pancreatic hormones allowed us to have a clearer understanding of the observed interaction of glucagon and fructose. As expected, TPN markedly increased NHGU [26]. In infected animals in which we did not prevent compensatory changes in insulin and glucagon, chronic fructose infusion did not augment NHGU [27]. In the present study, changes in insulin and glucagon were prevented; and fructose was equally ineffective. If continuous infusion of fructose was equally effective in augmenting NHGU as an acute infusion of fructose, NHGU should have increased by approximately 17 μmol kg^{-1} min^{-1} [28,29]. The failure of continuous fructose infusion is unlikely to be due to a failure of fructose to sustain the translocation of GK or a compensatory fall in total GK activity, as acute discontinuation of a chronic fructose infusion markedly impaired NHGU [30]. Total hepatic GK activity tended to decrease and high doses of fructose can induce insulin resistance [31]. However, given that fructose infusion increased hepatic glycogen cycling and content, a compensatory decrease in total GK is unlikely to explain the failure of chronic fructose to augment NHGU. Fructose may be unable to chronically sustain an increase in NHGU if GK is not the prime determinant of NHGU in adapted settings. In contrast to acute regulation of glucose disposal where glycogen synthesis is a major metabolic fate, in continuous nutritional support, hepatic lactate release and glucose oxidation are the main metabolic fates. Thus, for continuous fructose to sustain an increase in NHGU, hepatic glycolytic capacity would have to increase in parallel with any increase in glucose phosphorylation capacity [29,32]. Although fructose via activation of 6-phosphofructose-1-kinase can augment glycolysis [11], it is possible that glycolysis was already maximally activated by the TPN.

Continuous fructose infusion was also unable to reverse the inhibition of NHGU by continuous glucagon infusion. As we had seen previously, continuous infusion of glucagon decreased liver glucose uptake and lactate release during TPN [19]. The failure of fructose to augment NHGU in the absence of glucagon infusion cannot be explained by the possibility that NHGU was already maximally activated because NHGU can increase further [20]. The glucagon-mediated decrease in NHGU was not accompanied by a decrease in GK. Interestingly, fructose infusion was able to augment total GK activity in the liver and was able to modestly increase glycogen cycling even in the presence of glucagon. Thus, stress hormones like glucagon probably exert their greatest effect on liver glucose uptake at a site distal to GK and 6-phosphofructo-1-kinase. We tried to activate pyruvate kinase by combining fructose and xylitol infusion in a group of (n = 5) studies [33]. However, liver dysfunction developed as evidenced by an increase in plasma bilirubin. The protocol was discontinued. A recent report indicates a similar complication with xylitol in dogs [34].

Continuous fructose infusion impaired glucagon-stimulated net hepatic alanine uptake. Glucagon is a potent stimulator of net hepatic alanine fractional extraction [35,36]. Interestingly, in the absence of glucagon infusion, fructose increased net hepatic alanine fractional extraction but attenuated the glucagon-mediated increase. The

mechanism for the decrease in net hepatic alanine fractional extraction is unclear.

Fructose did not impair glucagon-stimulated liver NEFA uptake. Nonesterified fatty acid is the major fuel oxidized by the liver and can modulate the suppression of glucose production by insulin. Our recent work indicates that NEFAs interact with glucagon to impair NHGU during TPN [21]. In the present study, NEFA uptake and fractional extraction by the liver were increased, despite only modest changes in circulating NEFA concentrations.

In summary, although NHGU is enhanced when fructose is acutely infused, continuous fructose infusion is unable to augment NHGU even if pancreatic compensation is prevented. Moreover, fructose is equally ineffective when liver glucose uptake is impaired by the continuous administration of glucagon. Thus, the beneficial effects of fructose (or its target GK) on hepatic glucose uptake are short lived and would not likely be of therapeutic use in the long-term treatment of stress-induced hyperglycemia encountered in the nutritionally supported setting.

Acknowledgment

We gratefully acknowledge the technical support provided by Amy Nunnally, Jaime Adcock, Eric Nass, Doss Neal, Ben Farmer, and the Diabetes Research and Training Center Hormone and Analytical Services Core and Metabolic Physiology Shared Resource Core in these studies.

These studies were funded from the following sources: National Institutes of Health DK43748 (PI: Owen McGuinness), National Institutes of Health DK20593 (Diabetes and Research and Training Center), and American Diabetes Association (PI: Owen McGuinness).

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