Portal Venous Hyperinsulinemia Does Not Stimulate Gut Glucose Absorption in the Conscious Dog

Raul C. Camacho, Joshua C. Denny, R. Richard Pencek, Yoshiharu Koyama, D. Brooks Lacy, Freyja D. James, and David H. Wasserman

The purpose of the present study was to assess whether physiological portal vein hyperinsulinemia stimulates gut glucose absorption in vivo. Chronically catheterized (femoral artery, portal vein, inferior vena cava, and proximal and distal duodenum) and instrumented (Doppler flow probe on portal vein) insulin (INS, 2 mU · kg^{-1} · min^{-1}, n = 6) or saline (SAL, n = 5) infused dogs were studied during basal (30 minutes) and experimental (90 minutes) periods. Arterial and portal vein plasma insulin were 3.3- and 3.2-fold higher, respectively, throughout the study in INS compared to SAL. An intraduodenal glucose infusion of 8 mg · kg^{-1} · min^{-1} was initiated at t = 0 minutes. At t = 20 and 80 minutes, a bolus of 3-*O*-[^{3}H]methylglucose (MG) and L-[^{14}C]glucose (L-GLC) was injected intraduodenally. Phloridzin, an inhibitor of the Na^{+}-dependent glucose transporter (SGLT1), was infused from t = 60 to 90 minutes in the presence of a peripheral isoglycemic clamp. Net gut glucose output (NGGO) was 5.2 ± 0.6 and 4.6 ± 0.8 mg · kg^{-1} · min^{-1} in INS and SAL, respectively, from t = 20 to 60 minutes. Transporter-mediated absorption was 87% ± 2% of NGGO in both INS and SAL. Passive gut glucose absorption was 13% ± 2% of NGGO in both INS and SAL. Phloridzin-induced inhibition of transporter-mediated absorption completely abolished passive absorption of L-GLC in both groups. This study shows that under physiological conditions, a portal vein insulin infusion that results in circulating hyperinsulinemia does not increase either transporter-mediated or passive absorption of an intraduodenal glucose load.

GUT GLUCOSE absorption occurs via both transporter-mediated and passive processes. Transporter-mediated absorption of glucose across the intestinal cell wall occurs via luminal Na^{+}-dependent glucose transporter (SGLT1) and facilitative glucose tranporter (GLUT2).[1-3] Passive transport occurs via paracellular diffusion across the intestinal wall. Data from studies investigating the effect of hyperinsulinemia on gut glucose absorption have been conflicting. Intraportal insulin infusion in isolated, perfused rat intestine and liver[4] and in situ studies in anesthetized rats[5] have both shown that hyperinsulinemia increases gut glucose absorption. However, studies in isolated jejunal loops[6] have found that hyperinsulinemia has no effect on net jejunal glucose uptake. Both stimulatory[5] and inhibitory[6] effects of hypoinsulinemia on gut glucose absorption have been reported. Studies have shown that glucocorticoid analogs[7,8] (glucocorticoids are high during stress), anesthesia, and bowel manipulation[9] affect gut glucose absorption. To circumvent these complications, our laboratory has employed a method of assessing transporter-mediated and passive gut glucose absorption in the conscious, unstressed state[10] that is an extension of a technique described for rats by Uhing and Kimura.[11] Our model allows isotopic methods to be performed in conjunction with arterial, portal, and hepatic venous, and intraduodenal sampling. Blood flows are measured, and an effort is made to study absorption in the presence of tightly controlled arterial glucose.

The present study was designed to test the hypothesis that physiological portal venous hyperinsulinemia stimulates gut glucose absorption and entry to the blood glucose pool in an unstressed in vivo model, ie, the conscious dog. Radioactive tracers were used to differentiate passive and transporter-mediated pathways for glucose absorption. The conscious dog model circumvents many of the complications of previous investigations performed in situ or in vitro, allowing for physiological assessment of intestinal nutrient absorption in response to insulin.[1] Whether physiological portal venous hyperinsulinemia stimulates gut glucose absorption may have important implications in developing strategies for islet implantation and use of insulin delivery systems in people with diabetes.

MATERIALS AND METHODS

Animal Care and Surgical Procedures

Eleven mongrel dogs of either gender with a mean weight of 23 ± 1 kg were studied. The dogs were housed in a facility that met the American Association for the Accreditation of Laboratory Animals Care guidelines. All procedures were approved by the Vanderbilt University Animal Care and Use Committee. The dogs were fed a standard diet of meat and dry food (34% protein, 14.5% fat, 46% carbohydrate, and 5.5% fiber based on dry weight). At least 16 days before each experiment, a laparotomy was performed under general anesthesia. Two silastic catheters (0.03 mm inner diameter [ID]) were inserted into the inferior vena cava for indocyanine green (ICG) and glucose infusions. Silastic catheters (0.04 mm ID) were inserted into the portal vein and left common hepatic vein for blood sampling as described previously. Two silastic catheters (0.03 mm ID) were inserted into the duodenum. The first catheter was inserted just below the pyloric sphincter for administration of glucose, phloridzin, 3-*O*-[^{3}H]methylglucose (MG), and L-[^{14}C]glucose (L-GLC). The second duodenal catheter was inserted approximately 10 cm caudal from the infusion catheter (just before the junction of the duodenum with the jejunum). A silastic catheter (0.03 mm ID) was inserted into the left femoral artery

From the Department of Molecular Physiology & Biophysics and Diabetes Research and Training Center, Vanderbilt University School of Medicine, Nashville, TN.

Submitted August 4, 2003; accepted May 8, 2004.

Supported by National Institutes of Health Grant No. R01-DK-50277 and Diabetes Center Grant No. DK-20593.

Address reprint requests to Raul C. Camacho, Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN 37232.

0026-0495/04/5310-0007$30.00/0

doi:10.1016/j.metabol.2004.07.002

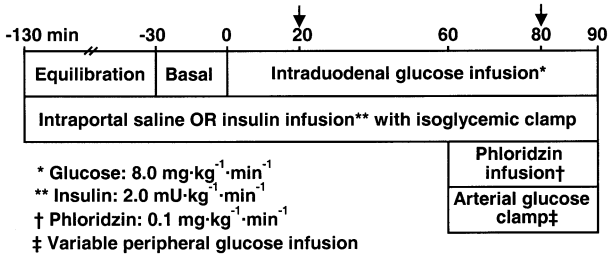

Fig 1. Experimental protocol. Arrows indicate the injection of a tracer bolus (25 μCi at t = 20 minutes and 100 μCi at t = 80 minutes) of MG and L-GLC into the duodenum. Glucose was infused in the duodenum in the absence (t = 0 to 60 minutes) or presence (t = 60 to 90 minutes) of phloridzin. From t = 60 to 90 minutes, a variable peripheral glucose infusion was used to maintain arterial glucose concentrations at levels seen prior to the phloridzin infusion.

for blood sampling. After insertion, the vascular catheters were filled with saline containing heparin and knotted at the free ends.

Doppler flow probes (Transonic Systems, Ithaca, NY) were used to measure portal vein and hepatic artery blood flows. A section of the portal vein upstream from the gastroduodenal vein was cleared of tissue and fitted with a 6.0-mm ID flow cuff. A section of the hepatic artery was fitted with a 3.0-mm ID flow cuff. The flow probe leads and knotted catheter ends were stored in a subcutaneous pocket made in the abdominal region. The femoral artery catheter was stored in a pocket in the inguinal region. Only those animals that met the following criteria were used in this study: leukocyte count less than 18,000/μL, hematocrit greater than 0.36 by volume, normal stools, and a good appetite (consuming the entire daily ration). Animals that met these criteria were fasted 18 hours prior to the beginning of the study to insure they were in the postabsorptive state.

Experimental Protocol

The experimental protocol is shown in Fig 1. On the day of the experiment, the catheters and flow probes were freed from subcutaneous pockets using approximately 2-cm incisions made after application of 2% lidocaine. Saline was infused into the arterial sampling catheter throughout the duration of the study. Animals were placed in a Pavlov stand and given time to acclimate to the laboratory (t = −190 to −130 minutes). At t = −130 minutes, a venous infusion of ICG and a portal infusion of either saline (n = 5, SAL) or insulin (n = 6, 2 mU · kg^{-1} · min^{-1}, INS) was initiated and continued for the duration of the study in the presence of an isoglycemic clamp in INS to match glucose concentrations seen in SAL. The ICG infusion served as a backup measurement of splanchnic blood flow in case the Doppler probes did not function properly. There was no Doppler flow probe failure in these studies. From t = −30 to 0 minutes, blood samples were taken for the assessment of baseline measurements. The duodenum was empty during this period and no sample could be obtained. At t = 0 minutes, the experimental period began with an intraduodenal primer of glucose (150 mg · kg^{-1}) followed by a continuous intraduodenal infusion of 8 mg · kg^{-1} · min^{-1} for the remainder of the study. The rate of the intraduodenal glucose infusion was chosen to reproduce glucose levels commonly seen in the portal vein following feeding.[12] At t = 20 minutes, a bolus containing MG (absorbed via active, facilitative, and passive routes) and L-GLC (absorbed passively) was injected (25 μCi of each isotope) into the duodenum. At t = 60 minutes, an intraduodenal primer of phloridzin (1.97 mg · kg^{-1}) was given followed by a continuous intraduodenal infusion of 0.103 mg · kg^{-1} · min^{-1} for the remainder of the study. At the start of the phloridzin infusion, the isoglycemic clamp was continued to maintain the arterial glucose concentration at the level seen before phloridzin infusion in both SAL and INS. At t = 80 minutes, a second bolus of MG and L-GLC (100 μCi of each isotope), 4-fold larger than the first, was introduced into the duodenum. During the experimental period (t = 0 to 90 minutes), blood and duodenal samples were taken every 10 minutes. In addition to these samples, blood and duodenum samples were taken every minute for 5 minutes following administration of each tracer bolus. At the end of the experiment animals were euthanized with sodium pentobarbital and an autopsy was performed to confirm catheter placement.

Blood and Intraduodenal Sample Analyses

Plasma and intraduodenal glucose levels were determined on the day of the experiment using the glucose oxidase method with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Those plasma samples, which were not immediately analyzed, were stored at −70°C for later analysis. Whole blood and intraduodenal samples were deproteinized with barium hydroxide and zinc sulfate to assess the radioactivity of MG and L-GLC in blood and duodenal samples. After centrifugation, the supernatant was dried and reconstituted in 1 mL of water and 10 mL Ultima Gold scintillant (Packard, Meriden, CT). Radioactivity was determined using a Packard TRI-CARB 2900TR liquid scintillation counter. Plasma insulin and glucagon and blood glucose were measured as described previously.[13]

Calculations

Total net gut glucose output (NGGO) was determined using Equation 1.

$$\text{NGGO} = ([\text{P}] - [\text{A}]) \cdot \text{PVF} \quad (1)$$

[P] and [A] represent portal vein and arterial glucose concentrations, respectively, and PVF is portal vein blood flow. Calculations of the transporter-mediated and passive components of gut glucose absorption are based on tracer and glucose data obtained during the 5 minutes of sampling following administration of the tracer bolus. Due to uncertainties regarding bolus mixing, catheter position, and intestinal transit time, the percentage contributions of transporter-mediated and passive gut glucose absorption were calculated using 3 different equations.[10] Previous work has shown that the calculation of the passive fraction of gut absorption via both direct and indirect assessment of intraduodenal radioactivity yields the same results.[10] The direct approach was used in the present study (Equation 2) to calculate the passive fraction of gut glucose absorption.

Fraction of intestinal glucose transport that is passive

$$= \frac{(\text{L-GLC}_\text{P} - \text{L-GLC}_\text{A})}{(\text{MG}_\text{P} - \text{MG}_\text{A})} \cdot \frac{\text{MG}_\text{D}}{\text{L-GLC}_\text{D}} \quad (2)$$

L-GLC_P and L-GLC_A represent the portal venous and arterial radioactivity of L-[^{14}C]glucose, respectively. MG_P and MG_A represent the portal venous and arterial radioactivity of 3-*O*-[^{3}H]methylglucose, respectively. MG_D and L-GLC_D represent the duodenal radioactivities of 3-*O*-[^{3}H]methylglucose and L-[^{14}C]glucose, respectively. The rates of transporter-mediated and passive absorption were calculated by multiplying the fraction of passive and transporter-mediated absorption by NGGO (Equations 3 and 4, respectively).

Net rate of transporter-mediated absorption

$$= (1 - \text{Passive fraction}) \cdot \text{NGGO} \quad (3)$$

$$\text{Net rate of passive absorption} = \text{Passive fraction} \cdot \text{NGGO} \quad (4)$$

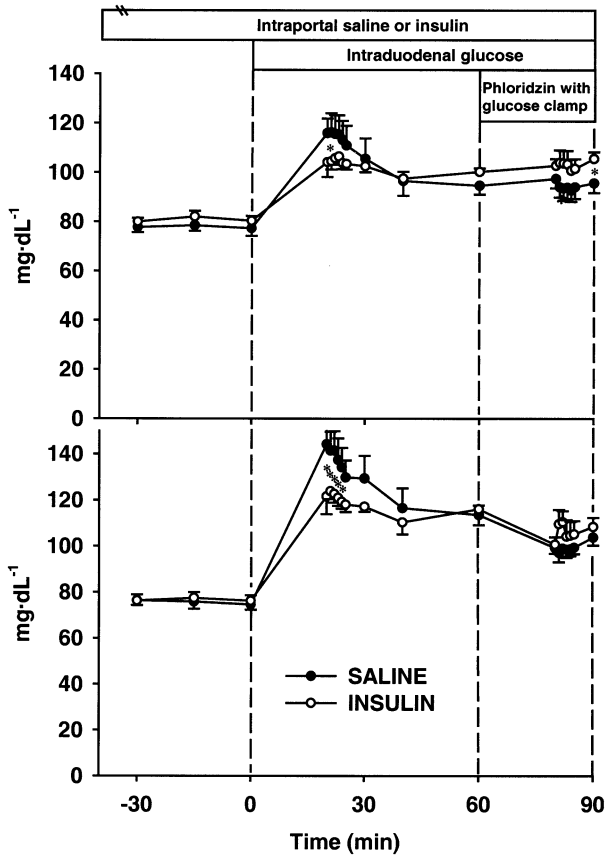

Fig 2. (A) Arterial and (B) portal vein blood glucose concentrations in SAL (●) and INS (○) during the baseline sampling period (−30 to 0 minutes) and intraduodenal glucose infusion period in the absence (0 to 60 minutes) and presence (60 to 90 minutes) of intraduodenal phloridzin. Data are means ± SE. *$P < .05$.

Statistics

All data are presented as the mean ± SE. Analysis of variance ANOVA was performed to assess differences between gut absorption, hormone, and substrate concentrations over time. Paired *t* tests were used to determine differences between absorption with and without the intraduodenal phloridzin infusion. Differences were considered significant at $P < .05$.

RESULTS

Blood and Duodenal Glucose and Glucose Infusion Rate

Arterial (81 ± 1 and 78 ± 1 mg · dL^{-1} in INS and SAL, respectively, Fig 2A) and portal vein (77 ± 1 and 76 ± 1 mg · dL^{-1} in INS and SAL, respectively, Fig 2B) blood glucose levels were similar between groups during the basal period. A sample could not be obtained from the duodenum during the basal period, as the animals were postabsorptive. During the intraduodenal glucose infusion (from t = 20 to 60 minutes), mean arterial (103 ± 1 and 109 ± 2 mg · dL^{-1} in INS and SAL, respectively) and portal vein (119 ± 1 and 132 ± 3 mg · dL^{-1} in INS and SAL, respectively, $P < .05$) blood glucose levels increased. During the phloridzin infusion, arterial blood glucose levels did not significantly change from the levels seen prior to the phloridzin infusion due to the isoglycemic clamp and were similar between groups except at t = 90 minutes, when the concentration in SAL was lower. Portal vein blood glucose decreased during the phloridzin infusion to 106 ± 2 and 99 ± 1 mg · dL^{-1} in INS and SAL, respectively. Duodenal glucose was not significantly different during the phloridzin infusion. To maintain isoglycemia, the glucose infusion rate was significantly greater in INS compared to SAL throughout the study (Table 1). The rise in arterial blood glucose seen in both groups during the intraduodenal glucose infusion occurred without the need to alter the glucose infusion rate in the INS group.

Table 1. Plasma Insulin, Glucagon, Cortisol, Catecholamines, Portal Vein Blood Flow, and Glucose Infusion Rate During the Delivery of an Intraduodenal Glucose Load in the Absence or Presence of Phloridzin in SAL and INS

Variable	Group	Baseline (−30 to 0 min)	Intraduodenal Glucose Load	
			−Phloridzin (0 to 60 min)	+Phloridzin (60 to 90 min)
Glucose infusion rate (mg · kg^{-1} · min^{-1})	SAL	—	—	5 ± 1
	INS	15 ± 3*	16 ± 3*	22 ± 2*
Arterial insulin (μU · mL^{-1})	SAL	7 ± 1	29 ± 6	18 ± 4
	INS	67 ± 12*	83 ± 12*	87 ± 19*
Portal vein insulin (μU · mL^{-1})	SAL	33 ± 10	64 ± 15	50 ± 18
	INS	195 ± 25*	192 ± 28*	185 ± 31*
Arterial clucagon (pg · mL^{-1})	SAL	26 ± 3	24 ± 3	25 ± 4
	INS	31 ± 3	28 ± 1	30 ± 2
Portal vein blood flow (mL · kg^{-1} · min^{-1})	SAL	23 ± 1	26 ± 1	25 ± 3
	INS	29 ± 1	32 ± 1	32 ± 1
Arterial cortisol (μg · dL^{-1})	SAL	3.4 ± 0.7	3.8 ± 0.3	5.7 ± 0.8
	INS	2.6 ± 0.4†	3.5 ± 0.5†	7.1 ± 0.8
Arterial epinephrine (pg · mL^{-1})	SAL	228 ± 60	227 ± 65	282 ± 120
	INS	161 ± 26	163 ± 19	176 ± 45
Arterial norepinephrine (pg · mL^{-1})	SAL	228 ± 37	239 ± 30	234 ± 54
	INS	181 ± 13	211 ± 16	201 ± 25

Note. Values are mean ± SE.

*$P < .05$ *v* SAL.

†$P < .05$ *v* intraduodenal + phloridzin.

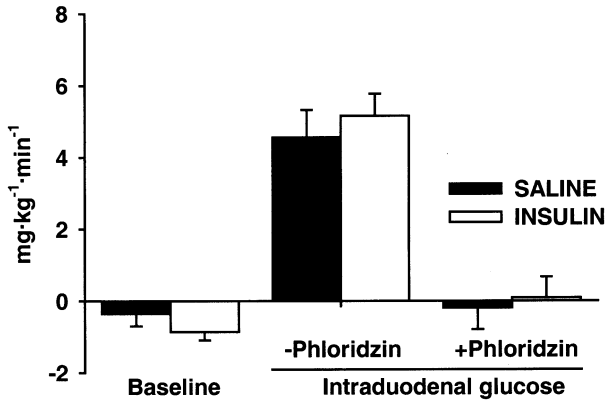

Fig 3. Net gut glucose output in SAL (■) and INS (□) during the baseline period and intraduodenal glucose infusion period in the absence and presence of phloridzin. Negative values represent the uptake of glucose from the gut. Data are means ± SE.

Plasma Hormones and Portal Vein Blood Flow

Plasma hormones and portal vein blood flow are shown in Table 1. Mean arterial plasma insulin levels were 3.3-fold higher in INS versus SAL throughout the study. Mean portal vein plasma insulin levels were 3.2-fold higher in INS versus SAL throughout the study. Arterial plasma glucagon did not significantly change from basal levels during the intraduodenal glucose load or phloridzin infusion periods in either group. Portal vein blood flow did not change throughout the study in either group, but tended to be higher in INS throughout the study ($P = .05$). Hepatic artery blood flow was not different between groups throughout the study (data not shown). Arterial plasma cortisol was significantly increased in INS during phloridzin infusion, but was not different between groups throughout the study. Arterial catecholamines were not different between groups throughout the study.

Transporter-Mediated and Passive Fractions of Gut Absorption

During the intraduodenal glucose infusion passive gut glucose absorption was determined to be 13% ± 22% in both INS and SAL (ie, transporter-mediated absorption was 87% ± 2% in both INS and SAL; data not shown).

NGGO, Net Transporter-Mediated and Passive Glucose Absorption, and Phloridzin-Blocked Glucose Absorption

NGGO is shown in Fig 3. Prior to the onset of the intraduodenal glucose, NGGO was slightly negative (-0.9 ± 0.2 and -0.4 ± 0.4 mg · kg^{-1} · min^{-1} in INS and SAL, respectively). During the intraduodenal glucose infusion, NGGO increased to approximately 5.2 ± 0.6 and 4.6 ± 0.8 mg · kg^{-1} · min^{-1} in INS and SAL, respectively. Transporter-mediated (4.5 ± 0.6 and 3.9 ± 0.6 mg · kg^{-1} · min^{-1} in INS and SAL, respectively) and passive absorption (0.6 ± 0.1 and 0.6 ± 0.2 mg · kg^{-1} · min^{-1} in INS and SAL, respectively) were similar between groups (Fig 4). The intraduodenal phloridzin infusion virtually abolished NGGO (0.0 ± 0.3 and -0.2 ± 0.6 mg · kg^{-1} · min^{-1}, in INS and SAL, respectively) as rates were not significantly different than zero from t = 70 to 90 minutes. We did not account for lymph drainage contributing to NGGO, as the lymphatic system plays an insignificant role in transport of meal-derived glucose in the conscious dog.[12]

DISCUSSION

The present study shows that short-term exposure to physiological portal venous hyperinsulinemia does not stimulate either transporter-mediated or passive gut glucose absorption in the conscious, unstressed dog. The method of assessing transporter-mediated and passive gut glucose absorption presented here is an extension of the method described by Uhing and Kimura[11] that we have previously adapted for use in the dog model.[10,14] The experimental protocol takes advantage of arterial-venous and duodenal sampling techniques, as well as isotopic tracer methodology, to determine the contributions of transporter-mediated and passive processes to the absorption of an intraduodenal glucose load in dogs.

NGGO is comprised of transporter-mediated and passive pathways. Transporter-mediated absorption occurs via SGLT1,[1-3] while passive transport occurs via paracellular diffusion across the intestinal wall. Recent studies have described a mechanism for gut glucose absorption that involves GLUT2-mediated facilitated diffusion.[15,16] The methods used here are able to measure NGGO and distinguish between SGLT1 and passive transport of glucose, but not that of GLUT2. Although effects of pharmacological insulin levels on gut glucose absorption in isolated jejunal loop[6] or perfused organ preparations[4,5] have been investigated, effects of physiological hyperinsulinemia on transporter-mediated and passive pathways of gut glucose absorption in a conscious, unstressed state have not been studied.

The insulin infusion rate of 2 mU · kg^{-1} · min^{-1} was chosen because it results in an insulin concentration that is physiological, but still high enough to ensure a significantly greater insulin concentration than that observed during an intraduodenal glucose infusion alone. NGGO and its transporter-mediated or passive components were not affected by the presence of portal venous hyperinsulinemia (Figs 3 and 4). The fact that there was no need to alter the glucose infusion rate (Table 1)

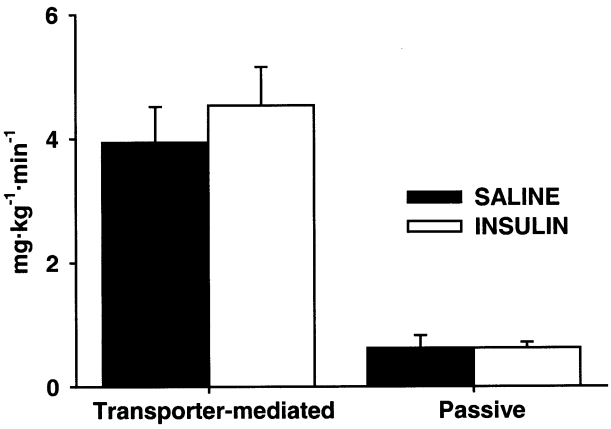

Fig 4. The rate of transporter-mediated and passive gut glucose absorption in SAL (■) and INS (□) during the intraduodenal glucose infusion period. Data are means ± SE.

with the onset of the intraduodenal glucose infusion indirectly supports the observation that hyperinsulinemia has no effect on gut glucose absorption or the processes that comprise it. Phloridzin is a potent inhibitor of SGLT1, and was infused to test the dependence of any increase in glucose absorption on this transporter during physiological hyperinsulinemia. Phloridzin eliminated not only transporter-mediated glucose absorption, but also passive absorption in INS and SAL, as NGGO was not different than zero (Fig 3). This observation is consistent with previous findings from our laboratory[10,14] and others,[17,18] that all of the pathways of gut glucose absorption are either directly or indirectly dependent on SGLT1-mediated transport, and extends this finding to the condition of physiological portal venous hyperinsulinemia.

During the intraduodenal glucose infusion period, portal vein insulin concentrations were at a high physiological level of approximately 140 $\mu U \cdot mL^{-1}$, compared to the pharmacological and suprapharmacological doses of approximately 330, 1,700, and 17,000 $\mu U \cdot mL^{-1}$ used in the study by Stumpel et al.[4] The extremely high insulin levels used could possibly explain the difference in the results of their study, in which they found that portal vein insulin caused an acute increase in intestinal glucose absorption, and ours. Additionally, their study was conducted in an isolated perfused organ preparation, as opposed to our conscious, unstressed dog model. Data from studies investigating the effect of glucocorticoid analogs on gut glucose absorption have been conflicting. Both stimulatory[8] and inhibitory[19] effects of dexamethasone on gut glucose absorption have been reported. Additionally, other studies have shown that anesthesia and surgical bowel manipulation[9] affect gut glucose absorption. The effect of these nonphysiological manipulations may also explain why Westergaard[5] concluded that elevated plasma insulin (>200 $\mu U \cdot mL^{-1}$) increases glucose transport in isolated rat jejunal loop. Our results are consistent with those of Kellet et al,[6] in which rats were injected with a 24-U/kg dose of insulin. They saw no change in absorption of the nonmetabolizable glucose analogue, MG, in isolated jejunal loops. It is important to note that the model in our studies directly assesses the rates of appearance of glucose and glucose analogues in the portal vein (as opposed to the disappearance from isolated jejunal loops[6]) and can thereby quantify not only the passive and transporter-mediated fractions but also the absolute net rates of absorption from the intestine. Although MG and D-glucose are both actively transported by the SGLT1 with a similar V_{max} and K_m,[11,20,21] it is conceivable that estimates of the rate of trace amounts of MG transport could be competitively inhibited by high duodenal D-glucose. We do not think competition was a factor because the ratio of these 2 sugars did not change between the duodenum and portal vein. It is important to note that in rats at least, transporter-mediated absorption predominates over a D-glucose range of 90 to 7,200 $mg \cdot dL^{-1}$.[9]

An unexpected finding of this study was that portal vein blood flow tended to be higher in INS compared to SAL, throughout the study ($P = .05$). This is consistent with previous literature regarding insulin's hemodynamic effects in other vascular beds.[22,23] After observing increases in blood flow in initial INS experiments, particular attention was paid to this increase with the onset of insulin infusion in subsequent experiments. A greater than 5 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in portal vein blood flow was consistently seen with the onset of portal vein insulin infusion. NGGO is dependent on portal vein blood flow and arterial-portal venous blood glucose differences. As a consequence of the increased blood flow in INS, the arterial-portal venous blood glucose difference was slightly reduced (16 ± 1 $mg \cdot dL^{-1}$ in INS and 18 ± 1 $mg \cdot dL^{-1}$ in SAL; P = not significant), resulting in the similar rates of NGGO that were observed.

In summary, a physiological increment in portal venous insulin does not stimulate NGGO, nor its transporter-mediated or passive components, in conscious, unstressed dogs. Physiological portal venous hyperinsulinemia tends to increase portal vein blood flow, which could aid in deposition and storage of carbohydrates to the liver in the postprandial setting, despite not affecting gut glucose absorption itself.

ACKNOWLEDGMENT

We would like to thank the Hormone Assay and Animal Resources Cores of the Vanderbilt Diabetes Research and Training Center for providing the hormone and catecholamine data.

REFERENCES

1. Ferraris RP, Diamond J: Regulation of intestinal sugar transport. Physiol Rev 77:257-302, 1997

2. Cheeseman CI: GLUT2 is the transporter for fructose across the intestinal basolateral membrane. Gastroenterology 105:1050-1056, 1993

3. Hediger MA, Coady MJ, Ikeda TS, et al: Expression cloning and cDNA sequencing of the Na^+/glucose co-transporter. Nature 330:379-382, 1987

4. Stumpel F, Kucera T, Gardemann A, et al: Acute increase by portal insulin in intestinal glucose absorption via hepatoenteral nerves in the rat. Gastroenterology 110:1863-1869, 1996

5. Westergaard H: Insulin modulates rat intestinal glucose transport: Effect of hypoinsulinemia and hyperinsulinemia. Am J Physiol 256: G911-G918, 1989

6. Kellett GL, Jamal A, Robertson JP, et al: The acute regulation of glucose absorption, transport and metabolism in rat small intestine by insulin in vivo. Biochem J 219:1027-1035, 1984

7. Thiesen A, Wild GE, Tappenden KA, et al: The locally acting glucocorticosteroid budesonide enhances intestinal sugar uptake following intestinal resection in rats. Gut 52:252-259, 2003

8. Stojanovska L, Rosella G, Proietto J: Dexamethasone-induced increase in the rate of appearance in plasma of gut-derived glucose following an oral glucose load in rats. Metabolism 40:297-301, 1991

9. Uhing MR, Kimura RE: The effect of surgical bowel manipulation and anesthesia on intestinal glucose absorption in rats. J Clin Invest 95:2790-2798, 1995

10. Pencek RR, Koyama Y, Lacy DB, et al: Transporter-mediated absorption is the primary route of entry and is required for passive absorption of intestinal glucose into the blood of conscious dogs. J Nutr 132:1929-1934, 2002

11. Uhing MR, Kimura REActive transport of 3-*O*-methyl-glucose by the small intestine in chronically catheterized rats. J Clin Invest 95:2799-2805, 1995

12. Moore MC, Pagliassotti MJ, Swift LL, et al: Disposition of a mixed meal by the conscious dog. Am J Physiol 266:E666-675, 1994

13. Hamilton KS, Gibbons FK, Bracy DP, et al: Effect of prior

exercise on the partitioning of an intestinal glucose load between splanchnic bed and skeletal muscle. J Clin Invest 98:125-135, 1996

14. Pencek RR, Koyama Y, Lacy DB, et al: Prior-exercise enhances passive absorption of intraduodenal glucose. J Appl Physiol 95:1132-1138, 2003

15. Kellett GL, Helliwell PA: The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of GLUT2 to the brush-border membrane. Biochem J 350:155-162, 2000

16. Helliwell PA, Richardson M, Affleck J, et al: Regulation of GLUT5, GLUT2 and intestinal brush-border fructose absorption by the extracellular signal-regulated kinase, p38 mitogen-activated kinase and phosphatidylinositol 3-kinase intracellular signaling pathways: implications for adaptation to diabetes. Biochem J 350:163-169, 2000

17. Pappenheimer JR, Reiss KZ: Contribution of solvent drag through intracellular junctions to absorption of nutrients by the small intestine of the rat. J Membr Biol 100:123-136, 1987

18. Pappenheimer JR, Volpp K: Transmucosal impedance of small intestine: Correlation with transport of sugars and amino acids. Am J Physiol 263:C480-C493, 1992

19. Chap Z, Jones RH, Chou J, et al: Effect of dexamethasone on hepatic glucose and insulin metabolism after oral glucose in conscious dogs. J Clin Invest 78:1355-1361, 1986

20. Fedorak RN, Thomson ABR, Porter VM: Adaptation of intestinal glucose transport in rats with diabetes mellitus occurs independent of hyperphagia. Can J Physiol Pharmacol 69:1143-1148, 1991

21. Wilson TH, Landau BR: Specificty of sugar transport by the intestine of the hamster. Am J Physiol 198:99-102, 1960

22. Baron AD: Hemodynamic actions of insulin. Am J Physiol 267:E187-E202, 1994

23. Clark MG, Wallis MG, Barrett EJ, et al: Blood flow and muscle metabolism: A focus on insulin action. Am J Physiol Endocrinol Metab 284:E241-258, 2003