Effect of enteral vs. parenteral glucose delivery on initial splanchnic glucose uptake in nondiabetic humans

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Received 18 April 2001; accepted in final form 25 March 2002

Vella, Adrian, Pankaj Shah, Rita Basu, Ananda Basu, Michael Camilleri, W. Frederick Schwenk, and Robert A. Rizza. Effect of enteral vs. parenteral glucose delivery on initial splanchnic glucose uptake in nondiabetic humans. Am J Physiol Endocrinol Metab 283: E259–E266, 2002. First published March 27, 2002; 10.1152/ajpendo.00178.2001.—To determine if enteral delivery of glucose influences splanchnic glucose metabolism, 10 subjects were studied when glucose was either infused into the duodenum at a rate of 22 μmol·kg⁻¹·min⁻¹ and supplemental glucose given intravenously or when all glucose was infused intravenously while saline was infused intraduodenally. Hormone secretion was inhibited with somatostatin, and glucose (~8.5 mmol/l) and insulin (~450 pmol/l) were maintained at constant but elevated levels. Intravenously infused [6,6-²H₂]glucose was used to trace the systemic appearance of intraduodenally infused [³-¹⁴C]glucose, whereas UDP-glucose flux (an index of hepatic glycogen synthesis) was measured using the acetoaminophen glucuronide method. Despite differences in the route of glucose delivery, glucose production (3.5 ± 1.0 vs. 3.3 ± 1.0 μmol·kg⁻¹·min⁻¹) and glucose disappearance (78.9 ± 5.7 vs. 85.0 ± 7.2 μmol·kg⁻¹·min⁻¹) were comparable on intraduodenal and intravenous study days. Initial splanchnic glucose extraction (17.5 ± 4.4 vs. 14.5 ± 2.9%) and hepatic UDP-glucose flux (9.0 ± 2.0 vs. 10.3 ± 1.5 μmol·kg⁻¹·min⁻¹) also did not differ on the intraduodenal and intravenous study days. These data argue against the existence of an “enteric” factor that directly (i.e., independently of circulating hormone concentrations) enhances splanchnic glucose uptake or hepatic glycogen synthesis in nondiabetic humans.

splanchnic glucose metabolism; postprandial hyperglycemia; acetoaminophen glucuronide; hepatic glycogen synthesis; enteric signal

GLUCOSE CONCENTRATIONS RARELY EXCEED 8.0–9.0 mmol/l in healthy nondiabetic humans. This is because of a complex interplay in the regulation of glucose metabolism between splanchnic and extrasplanchnic tissues. After carbohydrate ingestion, the splanchnic bed limits the amount of glucose that must be disposed of by peripheral tissues by a variety of mechanisms (20, 22, 24). These include metabolism of a portion of the ingested glucose by the gut, stimulation of hepatic glucose uptake, and suppression of hepatic (and perhaps renal) glucose production (1, 12, 36). The route of glucose delivery is also important. It is well established that glucose tolerance is better during enteral than during intravenous glucose delivery. This is in part because of increased insulin secretion mediated by neural (commonly referred to as the cephalic phase) and incretin pathways (4, 7, 21, 60). It is less clear whether enteral glucose administration directly (i.e., independently of changes in hormone concentrations) enhances splanchnic glucose uptake in humans.

Several studies suggest that it may. DeFronzo et al. (19) used the hepatic catheterization technique in an effort to determine whether the route of glucose delivery influences splanchnic glucose balance. They reported that net splanchnic balance markedly increased after glucose ingestion despite the fact that plasma glucose was maintained constant at ~12.5 mmol/l by means of a variable intravenous glucose infusion. Because tracers were not used in those experiments, the authors had to make a variety of assumptions to calculate net splanchnic glucose balance. The authors assumed that all ingested glucose was absorbed and that absorption was complete within the 3 h of study. They also assumed that splanchnic glucose uptake was not influenced by the higher insulin concentrations that were present after the glucose was ingested. Subsequent studies have shown that glucose absorption is not complete within 3 h of meal ingestion, that 10–20% of ingested glucose appears from 3 to 6 h after the start of the meal, and that not all of the ingested glucose actually reaches the portal venous system (11, 12, 23, 24, 37, 40, 41, 43, 52, 56). Furthermore, in the presence of hyperglycemia, increases in insulin substantially increase hepatic glycogen synthesis (5, 15). All of these factors would result in an overestimation of the effects of enteral administration on net splanchnic glucose balance. On the other hand, the authors assumed that endogenous glucose production was zero throughout the experiments, a situation that subsequent studies

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have shown rarely, if ever, occurs (6, 12, 14, 16, 52). This would have resulted in an underestimation of the effects of enteric glucose administration on splanchnic glucose uptake.

Although to our knowledge the study of DeFronzo et al. (19) is the only one that has compared the effects of enteral vs. intravenous glucose administration on splanchnic glucose uptake in humans, numerous studies have addressed this question in animals (8, 10, 17, 25, 30, 31, 34). Ishida et al. (34) demonstrated that hepatic glucose uptake in dogs was greater after oral or intraportal glucose than after intravenous glucose infusion. However, glucose and insulin concentrations also were higher after oral as opposed to intravenous glucose infusion. The Vanderbilt group has subsequently provided convincing evidence that hepatic glucose uptake in the presence of matched glucose, insulin, and glucagon concentrations is greater during intraportal than intravenous infusion (3, 25, 33, 47, 49, 50). This observation has subsequently been confirmed by other investigators in both rats (10, 13, 17, 30) and dogs (31, 34). These studies strongly support the existence of a portal signal. Interestingly, Bergman et al. (8) could detect no difference in splanchnic glucose uptake in dogs when glucose was infused enterally or directly into the portal vein. This argues against the existence of an independent enteral signal and suggests that enteral glucose infusion has the same effect on splanchnic glucose uptake as does portal glucose infusion.

The present experiments, undertaken as part of a series of experiments examining the regulation of splanchnic glucose metabolism (58, 59), offered the opportunity to reexamine this question in humans. Healthy nondiabetic subjects were studied on two occasions under conditions of hyperglycemia and hyperinsulinemia. On one occasion, all glucose was infused intravenously, and on the other occasion glucose was infused into the duodenum. Insulin concentrations were increased to ~450 pmol/l, whereas glucose concentrations were clamped at ~8.5 mmol/l. Somatostatin was given along with replacement amounts of glucagon and growth hormone so as to maintain portal venous hormone concentrations constant and equal in both groups.

We report that neither initial splanchnic glucose uptake (measured with a dual-tracer approach) nor UDP-glucose flux (measured using the acetaminophen glucuronide method) differed during enteral or intravenous glucose administration. These experiments demonstrate that, when glucose, insulin, and glucagon concentrations are matched, enteral glucose administration does not enhance initial splanchnic glucose uptake or accelerate hepatic glycogen synthesis in healthy nondiabetic humans.

METHODS

Subjects. After approval by the Mayo Institutional Review Board, 10 nondiabetic subjects gave informed written consent to participate in the study. Three were female, and seven were male. The subjects’ mean age was 36.7 ± 3.4 yr, weight 85.9 ± 5.8 kg, and body mass index 27.5 ± 1.1 kg/m². All subjects were in good health and at a stable weight. None regularly engaged in vigorous physical exercise. Before participation, all subjects completed a validated bowel disease questionnaire to ensure that they had no gastrointestinal symptoms (57).

Experimental design. The data from the enteral (58) and intravenous (59) infusions have been reported elsewhere; they were part of separate protocols examining the effects of glucagon-like peptide (GLP)-1 (58) and type 1 diabetes (59) on splanchnic glucose metabolism. By design, the order of the intravenous and enteral glucose infusions was random to permit comparison of the two routes. The experimental design has been described in detail previously (58, 59). In brief, subjects were admitted to the Mayo Clinic General Clinical Research Center at 1800 the evening before the study. After ingestion of a standard 10 kcal/kg meal (55% carbohydrate, 30% fat, and 15% protein), subjects fasted until the end of the study. At 0600 (−120 min) the next morning, subjects were taken to the fluoroscopy unit, where an 8-Fr Flexiilo enteral feeding tube (Ross Laboratories, Columbus, OH) was passed under fluoroscopic guidance via the nasopharynx into the fourth part of the duodenum. The average duration of tube placement was 15 min with an average fluoroscopy time of <2 min. The subjects were then returned to the Clinical Research Center. At 0745, subjects were asked to void, after which 2 g of acetaminophen suspension were administered over ~3 min via the nasoduodenal tube. Urine was then collected for the duration of the study to allow measurement of urinary acetaminophen glucuronide, as previously described (54).

At 0730, an 18-gauge cannula was inserted in a retrograde fashion in a dorsal hand vein. The hand was then placed in a heated box to obtain arterialized venous blood samples. An 18-gauge cannula was inserted in the other forearm to allow hormone and tracer infusion. At 0800 (0 min), a constant infusion of either glucose (22 μmol·kg⁻¹·min⁻¹) or saline at 0.5 ± 0.04 ml/min containing [3-H]glucose [812,983 ± 26,778 disintegrations (dpm)/min; New England Nuclear, Boston, MA] was started via the intraduodenal tube. Intravenous infusions of insulin (6 pmol·kg⁻¹·min⁻¹), somatostatin (60 ng·kg⁻¹·min⁻¹), human growth hormone (3 ng·kg⁻¹·min⁻¹), glucagon (0.65 ng·kg⁻¹·min⁻¹), [6,6-H₂]glucose (33 μmol·kg prime; 0.33 μmol·kg⁻¹·min⁻¹ constant; Masstrace, Woburn, MA), and [¹⁴C]galactose (15 μCi prime; 0.15 μCi/min constant; New England Nuclear) also were started at time 0. Additional glucose (enriched with [6,6-H₂]glucose) was infused intravenously in amounts sufficient to maintain plasma glucose concentration at ~8.5 mmol/l. In an effort to mimic the anticipated pattern of fall of glucose production and thereby maintain plasma glucose specific activity constant, the rate of the “basal” intravenous [6,6-H₂]glucose infusion was altered as follows: 0–30 min: 100%; 31–60 min: 86%; 61–90 min: 62%; 91–120 min: 46%; 121–150 min: 38%; 151–180 min: 30%; 181–210 min: 26%; and 211–240 min: 24%; see Ref. 48.

Analytical techniques. Arterialized plasma samples were placed in ice, centrifuged at 4°C, separated, and stored at −20°C until assay. Plasma glucose concentrations were measured using a glucose oxidase method (Yellow Springs Instrument, Yellow Springs, OH). Plasma insulin, cortisol, and growth hormone concentrations were measured using a chemiluminescence assay with reagents obtained from Beckman (Access Assay; Beckman, Chaska, MN). Plasma glucagon and C-peptide concentrations were measured by RIA (Linco Research, St. Louis, MO). Body composition was measured using dual-energy X-ray absorptiometry (DEXA scanner; Hologic, Waltham, MA). Plasma [3-H]glucose specific
activity was measured using liquid scintillation counting (53). Urinary [14C]glucuronide specific activity was measured using high-performance liquid chromatography (54). Plasma [6,6-2H2]glucose enrichment was measured by gas chromatography-mass spectrometry (38).

Calculations. Glucose appearance (Ra) and disappearance (Rd) were calculated employing the steady-state equations of Steele (55)

\[ R_d = R_a = \frac{F[D_{2glc}]}{MPE/[6,6-2H_2]glucose} - F[D_{2glc}] \]  

where \( F[D_{2glc}] \) is the intravenous infusion rate of [6,6-2H2]glucose, and MPE[6,6-2H2]glucose is the plasma enrichment of [6,6-2H2]glucose.

The systemic rate of appearance of intraduodenally infused [3-3H]glucose (duodenal Rd) was calculated as

\[ duodenal \ [3-3H]glucose \]  

\[ R_a = \frac{F[D_{2glc}][6,6-2H_2]glucose/[3-3H]glucose} \]

where [6,6-2H2]glucose and [3-3H]glucose are the plasma concentrations of each tracer.

Percent initial splanchnic [3-3H]glucose extraction (%SGE) was calculated as

\[ \text{%SGE} = \frac{G_{duod} - \text{duodenal [3-3H]glucose } R_a}{G_{duod}} \times 100 \]

where \( G_{duod} \) is the intraduodenal infusion rate of [3-3H]glucose, and duodenal[3-3H]glucose \( R_a \) is the systemic appearance of duodenally delivered [3-3H]glucose.

The systemic rate of appearance of intraduodenally infused glucose (duodenal \( R_a \)) on the intraduodenal glucose day was calculated by dividing the systemic rate of appearance (in dpm/min) of the intraduodenally infused [3-3H]glucose by the specific activity of the intraduodenally infused glucose

\[ \text{duodenal } R_a = \frac{\text{duodenal [3-3H]glucose } R_a}{\text{duodenal SA [3-3H]glucose}} \]

where duodenal SA [3-3H]glucose is the specific activity of the intraduodenally infused [3-3H]glucose. Endogenous glucose production was calculated by subtracting the sum of the rate of the intravenous glucose infusion and the systemic rate of appearance of intraduodenally infused glucose from the total glucose appearance rate.

Flux through the UDP-glucose pool was calculated as

\[ \text{UDP glucose flux} = \frac{F_{Gal}}{SA \text{ of UDP [14C]glucose}} \]

where \( F_{Gal} \) is the intravenous infusion rate of [14C]galactose and SA of UDP-[14C]glucose is the specific activity of acetaminophen [14C]glucuronide in the urine (27–29, 42). The assumptions and limitations of this technique have been previously discussed in detail (54).

Statistical analysis. Data in the text and Figs. 1–6 are expressed as means ± SE. Rates of infusion and turnover are expressed as micromoles per kilogram lean body mass per minute. The rates obtained during the last half-hour of the study were averaged and used for statistical analysis. Student’s two-tailed paired t-test was used to test the hypothesis that intraduodenal glucose infusion alters splanchnic glucose metabolism. A P value <0.05 was considered to be statistically significant.
day, whereas only radioactive glucose was infused intraduodenally on the intraduodenal saline day (Fig. 3B). This resulted in no difference in the total glucose infusion rates (Fig. 3C) on the intraduodenal glucose and intraduodenal saline study days (74.3 ± 5.2 vs. 75.1 ± 7.3 μmol·kg⁻¹·min⁻¹).

Plasma [6,6-²H₂]glucose enrichment and ratio of [6,6-²H₂]glucose to [3-³H]glucose. Intravenous infusion of [6,6-²H₂]glucose resulted in a prompt increase in plasma [6,6-²H₂]glucose enrichment (used to trace endogenous glucose production and glucose disappearance) on both study days to values that approximated steady state within 120 min (Fig. 4A). Because the intraduodenal glucose infusion did not contain [6,6-²H₂]glucose, whereas all intravenously infused glucose did, plasma [6,6-²H₂]glucose enrichment was slightly lower on the intraduodenal glucose than on intraduodenal saline study days. Intraduodenal infusion of [3-³H]glucose resulted in a slightly slower increase in plasma [3-³H]glucose concentration. This caused a transient increase in the plasma ratio of [6,6-²H₂]-glucose to [3-³H]-glucose (used to trace the systemic rate of appearance of intraduodenally infused [3-³H]-glucose) on both study days. This ratio fell to comparable levels that approximated steady state from 180 min onward on both study days (Fig. 4B).

Endogenous glucose production and glucose disappearance. Endogenous glucose production (3.9 ± 0.8 vs. 3.9 ± 0.9 μmol·kg⁻¹·min⁻¹) was comparably suppressed and glucose disappearance comparably stimulated (74.7 ± 5.3 vs. 79.0 ± 7.3 μmol·kg⁻¹·min⁻¹) on the intraduodenal glucose and intraduodenal saline study days (Fig. 5).

Initial splanchnic extraction and UDP-glucose flux. The systemic rate of appearance of the intraduodenally infused glucose averaged 17.7 ± 0.7 μmol·kg⁻¹·min⁻¹ during the intraduodenal glucose study day. Percent splanchnic extraction of intraduodenally infused

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**Fig. 2.** Plasma glucagon (A), growth hormone (B), and cortisol (C) concentrations observed during the study.

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**Fig. 3.** Intravenous glucose infusion rates necessary to maintain a constant plasma glucose concentration (A), the rate of intraduodenal glucose delivery (B), and the total rate of glucose delivery (C) observed during the study.

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**Fig. 4.** Plasma [6,6-²H₂]glucose enrichment (A) and the ratio of [6,6-²H₂]glucose to [3-³H]glucose (B) observed during the study.
DISCUSSION

Glucose tolerance is better after enteral as opposed to intravenous glucose administration. The present study indicates that, when arterial glucose, insulin, and glucagon concentrations are matched, enteral administration of glucose per se does not enhance initial splanchnic glucose extraction or increase flux through the UDP-glucose pool (and by implication, hepatic glycogen synthesis). Enteral glucose administration also does not alter the ability of glucose and insulin to suppress endogenous glucose production or stimulate glucose disappearance. These data therefore argue against the existence of an “enteric” signal that directly (i.e., independently of changes in circulating hormone concentrations) regulates splanchnic glucose metabolism in nondiabetic humans.

A variety of factors influence hepatic glucose uptake. Insulin stimulates hepatic glycogen synthesis, hyperglycemia inhibits glycogen breakdown, and glucagon antagonizes the effects of both (14, 18, 51). It therefore was important to ensure that arterial glucose, insulin, and glucagon concentrations did not differ during the intraduodenal and intravenous study days. Glucagon concentrations were maintained constant by infusing somatostatin along with “replacement” amounts of glucagon. Because we could not sample portal blood, we do not know the actual portal venous glucagon concentrations. However, this approach resulted in equal peripheral glucagon concentrations on the two study days. C-peptide was suppressed to almost undetectable levels, whereas the exogenous insulin infusion produced virtually identical plasma insulin concentrations on both occasions, thereby ensuring that portal insulin concentrations also were the same.

On the other hand, although arterial glucose concentrations also were equal, portal venous glucose concentrations must have been higher during intraduodenal glucose infusion. We therefore were surprised that initial splanchnic glucose uptake and flux through the UDP-glucose pool did not differ on the two occasions, since numerous studies has shown that a positive portal venous-to-hepatic venous glucose gradient stimulates hepatic glycogen synthesis. This effect has been referred to as the “portal” glucose signal. In a series of experiments, the Vanderbilt group has shown that generation of a portal venous-to-hepatic venous or hepatic arterial glucose gradient stimulates hepatic glucose uptake and suppresses extrahepatic glucose disposal (3, 32, 33, 50). This signal is abolished by hepatic denervation and is reproduced by ACh administration (2, 35, 44–46). The magnitude of the signal is determined by the size of the glucose gradient rather than by how much glucose is delivered to the liver. Pagliassotti et al. (50) have shown that the portal signal becomes detectable in dogs when the portal venous-to-hepatic venous gradient is ~1 mmol/l and is maximal when the gradient is ~4 mmol/l.

Fig. 5. Rates of glucose disappearance (A) and endogenous glucose production (B) observed during the study.

Fig. 6. Percent initial splanchnic glucose extraction (A) and UDP-glucose flux (B) observed during the study.
Because the present experiments were performed in human volunteers, we were unable to sample portal blood. We therefore do not know the size of the portal venous-to-hepatic venous glucose gradient that was generated by the intraduodenal glucose infusion. However, because glucose levels were at steady state, the range can be reasonably well defined. Glucose concentrations were clamped at ∼8.5 mmol/l. We have previously shown that splanchnic plasma flow averages ∼1 l/min under similar experimental conditions, which means that ∼8.5 mmol/min were entering the portal venous bed from the systemic circulation (6). The intraduodenal infusion rate was 22 µmol·kg⁻¹·min⁻¹ or ∼1.5 mmol/min. If all of the infused glucose reached the portal vein (which is unlikely), this would result in a portal glucose concentration of ∼9.75 mmol/l and a portal venous-to-hepatic venous glucose gradient of ∼1.25 mmol/l. On the other hand, initial splanchnic glucose extraction averaged ∼15%. Splanchnic glucose extraction represents the sum of losses resulting from incomplete glucose absorption, intestinal glucose metabolism, and hepatic glucose uptake (40, 41, 52). If hepatic glucose uptake were zero (which is also unlikely), this would mean that ∼1.25 mmol/min reached the portal vein, resulting in a portal venous glucose concentration of ∼9.38 and a gradient of ∼0.88 mmol/l. These calculations suggest that the portal venous gradient was close to or slightly above the gradient necessary to generate the portal signal in dogs (50). Therefore, either there is no portal signal in humans or the present experiments resulted in a portal signal that was close to the threshold value and therefore was not detected. Because a portal signal has been demonstrated in rats and dogs, we favor the latter explanation (9, 10, 13, 17, 30). In either case, the present experiments demonstrate that enteral delivery at the rate chosen does not enhance splanchnic glucose extraction.

Enteral delivery of glucose could have stimulated hepatic glycogen synthesis without altering initial splanchnic glucose extraction. This could occur if enteral delivery of glucose proportionately increased both glucose absorption and hepatic glycogen synthesis. The former would result in more glucose reaching the liver, whereas the latter would limit the amount of glucose that reached the systemic circulation. If both effects were equal, initial splanchnic glucose extraction might not differ during intraduodenal and intravenous glucose infusion. However, the comparable rate of flux through the UDP-glucose pool on the two study days argues against this explanation. Although this finding strongly suggests that hepatic glycogen synthesis was the same on both occasions, it does not rule out the possibility that hepatic glucose uptake was in fact greater during enteral glucose administration. This could occur if the resultant glucose 6-phosphate was selectively shunted away from glycolysis and toward glycosylation and/or lipid synthesis during intraduodenal glucose infusion (39). We know of no a priori reason why this should occur (26). Even if it did, the present data still indicate that neither initial splanchnic glucose extraction nor hepatic glycogen synthesis was influenced by the route of glucose delivery.

The current experiments suffer from several limitations. The most obvious is that only one intraduodenal glucose infusion rate was tested and glucose was infused in only the terminal portion of the duodenum. As discussed above, it is possible that different results would have been observed if the intraduodenal glucose infusion rate had been higher or if glucose had been infused in the proximal portion of the duodenum. This would create a greater portal venous-to-hepatic venous gradient, sufficient in magnitude to generate a “portal signal.” It is also possible that an effect on splanchnic glucose extraction and UDP-glucose flux was present; however, we did not have sufficient power to detect it because of the low intraduodenal glucose infusion rate. Splanchnic glucose extraction was higher in 4 of the 10 subjects on the intraduodenal saline than on the intraduodenal glucose study days. UDP-glucose flux was higher in 6 of the 10 subjects on the intraduodenal saline than on the intraduodenal glucose study days.

Splanchnic glucose extraction equals the sum of intestinal and hepatic glucose extraction. Splanchnic glucose extraction was slightly (but not significantly) higher during intraduodenal glucose administration (16.4 vs. 12.8%). Intestinal glucose extraction in dogs and pigs has been reported to range from 4 to 10% (1, 56). Therefore, hepatic glucose extraction in the present experiments could have ranged from 12.4 vs. 8.8 to 6.4 vs. 2.8%, respectively, on the intraduodenal glucose and saline study days. The latter calculation would imply a twofold increase in hepatic glucose uptake during intraduodenal glucose. If so, it apparently was not accompanied by an increase in hepatic glycogen synthesis, since UDP flux, if anything, was lower on the intraduodenal glucose study day.

Splanchnic glucose extraction was measured by tracing the systemic rate of appearance of intraduodenally infused [3-¹⁴C]glucose. Tracer alone was infused on the saline study day, since we were concerned that infusion of even a small amount of carrier glucose in the duodenum might elicit an enteric signal. It is therefore possible that metabolism of the tracer glucose in the gut was greater in the absence than in the presence of cold glucose, leading to an artificially high rate of splanchnic glucose extraction on the saline study day. The fact that the extraction ratio on the intravenous study day averaged 12.8%, whereas that previously reported by DeFronzo et al. (18) averaged ∼4%, is consistent with such a possibility. However, even if the splanchnic glucose extraction data are inaccurate, as noted above, the comparable rates of UDP-glucose flux on the two study days argues strongly against an “enteral” signal that enhances hepatic glycogen synthesis.

Insulin and glucagon were infused along with somatostatin to ensure comparable portal insulin and glucagon concentrations on the two study days. Plasma glucagon concentrations were the same before and after the start of the somatostatin and glucagon infusions. However, somatostatin, by inhibiting endogenous glucagon secretion, presumably reduced the portal-to-peripheral
GLUCOSE DELIVERY AND INITIAL SPLANCHNIC GLUCOSE UPTAKE

We therefore may have created relative hepatic hypoglycagoneemia on the two study days. This could have augmented splanchnic glucose uptake in both groups, potentially reducing the percent increase caused by enteric glucose delivery. Finally, it is possible that somatostatin interfered with the generation of the enteric signal. Somatostatin clearly does not ablate the portal glucose signal in dogs, since somatostatin has been consistently used in the experiments that have established the existence of this signal (50). However, Burcelin et al. (10) have recently reported that somatostatin prevents hypoglycemia that is otherwise observed when low doses of glucose are infused into the portal vein in mice. The hypoglycemic effect of infusing small amounts of glucose into the portal vein also appears to be blocked by knocking out GLUT2 transporters or by administration of a GLP-1 antagonist (9). It is currently not known whether a similar pattern of regulation occurs in humans or whether this putative portal signal is involved in the response to enterally delivered glucose.

In summary, under conditions in which arterial glucose, insulin, and glucagon concentrations are equal, initial splanchnic glucose extraction and hepatic glycogenesis are the same when glucose is infused intravenously or both intraduodenally and intravenously. These data indicate that the consistently better glucose tolerance observed in nondiabetic humans after glucose ingestion than after injection is likely because of the associated differences in insulin and glucagon concentrations and perhaps because of an increased portal venous-to-hepatic venous gradient rather than to the generation of an enteric signal that modulates splanchnic glucose metabolism.

We thank D. Burton and G. Thomforde for help with nasoduodenal tube placement; C. Etter, B. Dicke, C. Nordyke, and G. C. Ford for assistance; M. Davis for assistance in the preparation of the manuscript; and the staff of the Mayo General Clinical Research Center for assistance in performing the studies.

These experiments were supported by National Institutes of Health Grants DK-29953 and RR-00585 and the Mayo Foundation. P. Shah was supported by a research fellowship from Novo Nordisk and R. Basu by a research fellowship from the American Diabetes Association.

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E266

GLUCOSE DELIVERY AND INITIAL SPLANCHNIC GLUCOSE UPTAKE


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