Enteral infusion of glucose at rates approximating EGP enhances glucose disposal but does not cause hypoglycemia

Farhad Zangeneh, Rita Basu, Pankaj Shah, Puneet Arora, Michael Camilleri, and Robert A. Rizza

Divisions of *Endocrinology, Metabolism, and Internal Medicine and Nutrition and Gastroenterology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905

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Zangeneh, Farhad, Rita Basu, Pankaj Shah, Puneet Arora, Michael Camilleri, and Robert A. Rizza. Enteral infusion of glucose at rates approximating EGP enhances glucose disposal but does not cause hypoglycemia. Am J Physiol Endocrinol Metab 285: E280–E286, 2003; 10.1152/ajpendo.00055.2003.—Portal infusion of glucose at rates approximating endogenous glucose production (EGP) causes paradoxical hypoglycemia in wild-type but not GLUT2 null mice, implying activation of a specific portal glucose sensor. To determine whether this occurs in humans, glucose containing [3-3H]glucose was infused intraduodenally at rates of 3.1 mg·kg⁻¹·min⁻¹ (n = 5), 1.55 mg·kg⁻¹·min⁻¹ (n = 9), or 0.01 mg·kg⁻¹·min⁻¹ for 7 h in healthy nondiabetic subjects. [6,6-²H₂]glucose was infused intravenously to enable simultaneous measurement of EGP, glucose disappearance, and the rate of appearance of intraportal glucose infusion. Plasma glucose concentrations fell (P < 0.01) from 90 ± 1 to 84 ± 2 mg/dl during the 0/0.1 mg·kg⁻¹·min⁻¹ id infusions but increased (P < 0.001) to 104 ± 5 and 107 ± 3 mg/dl, respectively, during the 1.55 and 3.1 mg·kg⁻¹·min⁻¹ id infusions. In contrast, insulin increased (P < 0.05) during the 1.55 and 3.0 mg·kg⁻¹·min⁻¹ infusions, reaching a peak of 10 ± 2 and 18 ± 5 μU/ml, respectively, by 2 h. Insulin concentrations then fell back to concentrations that no longer differed by study end (7 ± 1 vs. 8 ± 1 μU/ml). This resulted in comparable suppression of EGP by study end (0.84 ± 0.2 and 0.63 ± 0.1 mg·kg⁻¹·min⁻¹). Glucose disappearance was higher (P < 0.01) during the final hour of the 3.1 than 1.55 mg·kg⁻¹·min⁻¹ id infusion (4.47 ± 0.2 vs. 2.6 ± 0.1 mg·kg⁻¹·min⁻¹), likely because of the slightly, but not significantly, higher glucose and insulin concentrations. We conclude that, in contrast to mice, selective portal glucose delivery at rates approximating EGP does not cause hypoglycemia in humans.

portal signal; splanchnic glucose extraction; glucose uptake; endogenous glucose production

PREVIOUS STUDIES IN ANIMALS (6, 11, 13, 15, 17, 18) and humans (9, 21) have provided compelling evidence for the existence of a portal glucose “sensor” that regulates both hepatic and peripheral glucose uptake. Enteric absorption of glucose causes concentrations to be higher in the portal vein than in the systemic circulation (2, 15). The resultant portal-to-hepatic venous glucose gradient has been reported to enhance hepatic glucose uptake and inhibit extrahepatic glucose disposal (2, 3, 10, 15, 18). Both hyperglycemia and hyperinsulinemia are required for the portal glucose “signal” to be detected (2, 10, 18). ACh activates and vagotomy or hepatic denervation abolishes the portal glucose signal, implying a neural origin (1, 23). In addition, infusion of glucose into the portal vein dampens the counterregulatory response to systemic hypoglycemia (14). Taken together, these data suggest that activation of the portal glucose sensor minimizes changes in portal and systemic glucose concentration.

The mechanism by which the portal vein senses glucose is an area of active investigation. Burcelin et al. (5–7), in an elegant series of experiments, have strongly implicated GLUT2 transporters in this process. They have shown that infusion of glucose in the portal vein of mice at a rate that approximated basal endogenous glucose production (EGP) markedly increased peripheral glucose clearance (7). This effect did not occur in mice in whom the GLUT2 transporter was knocked out and could be abolished by concurrent infusion of either somatostatin or the glucagon-like peptide (GLP)-1 antagonist exendin (5–7). In addition to providing interesting mechanistic insights, these studies were both surprising and provocative since intraportal glucose infusion caused a paradoxical fall in the plasma glucose concentration to hypoglycemic levels (5–7).

We have demonstrated previously that peripheral and splanchnic glucose uptake were the same in non-diabetic humans when glucose was infused intraduodenally or intravenously at a rate of 4 mg·kg⁻¹·min⁻¹ (24). However, in those experiments, glucose was clamped at ~150 mg/dl and insulin at ~400 pmol/l to stimulate hepatic and peripheral glucose uptake. Somatostatin had to be given to inhibit endogenous insulin secretion so as to ensure comparable portal insulin concentrations on both occasions. Somatostatin also has been given for the same reason in the animal experiments that have shown that intraportal glucose infusion decreases rather than increases extrahepatic glucose uptake (2, 8, 10, 18). Therefore, it is possible that use of somatostatin in ours and other investiga-

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Address for reprint requests and other correspondence: R. A. Rizza, Mayo Clinic Rochester, 200 1st St., SW, Rm. 5–194 Joseph, Rochester, MN 55905 (E-mail: rizza.robert@mayo.edu).
In a vein of the contralateral hand. The hand was then placed in a Plexiglas box maintained at 55°C to allow sampling of arterialized venous blood. At 0500, a primed continuous infusion of [6,6-3H]glucose was started and continued until the end of the study. At ~0630, the position of the nasoduodenal tube was confirmed by a portable abdominal radiography. At 0800 (0 min), a primed (12 µCi) continuous infusion (0.12 µCi/min) of [3-3H]glucose was infused in the duodenum via the nasoduodenal tube for the next 7 h. The [3-3H]glucose infusion also contained unlabeled glucose. In five subjects, glucose was infused in the duodenum at a rate of 3.1 mg·kg⁻¹·min⁻¹ on one occasion and 0.1 mg·kg⁻¹·min⁻¹ on the other occasion. In nine subjects, glucose was infused in the duodenum at a rate of 1.55 mg·kg⁻¹·min⁻¹ on one occasion and either saline (n = 4) or glucose (n = 5) at a rate of 1.22 mg·kg⁻¹·min⁻¹ (in error rather than saline) on the other occasion. The results of 1.22 mg·kg⁻¹·min⁻¹ infusion did not differ substantially from the 1.55 mg·kg⁻¹·min⁻¹ infusion and therefore are not presented as part of the current study but are available upon request. In addition, because results did not differ during the 0.1 mg·kg⁻¹·min⁻¹ id or saline alone infusions, these results were combined for purposes of analysis. Blood samples were collected at ~180, ~30, 0, 60, 120, 180, 210, 220, 230, 240, 270, 300, 330, 360, 390, and 420 min for analysis of tracer, hormone, and substrate concentrations.

**Experimental design.** Each subject was studied on two occasions separated by at least 1 wk. On the afternoon before each study, subjects were taken to the Mayo General Clinical Research Center where an 8-Fr Flexiflo enteral feeding tube (Ross Laboratories, Columbus, OH) was passed under fluoroscopic guidance via the nasopharynx for X-ray absorptiometry scan QDR4500 with fan scan technology.

**Calculations.** Rates of glucose appearance and disappearance were calculated using Steele’s non-steady-state equations (22). A pool volume of 200 ml/kg and a pool fraction of 0.65 were assumed. The systemic rate of appearance of the intraduodenally infused [3-3H]glucose was also calculated using Steele’s steady-state equations in which the plasma [3-3H]glucose concentration was substituted for the unlabelled glucose concentration (4). The systemic rate of appearance of [3-3H]glucose (in dpm·kg⁻¹·min⁻¹) was divided by the specific activity of the intraduodenally infused glucose (in dpm/mg) to convert the rates to milligrams per kilogram per minute. EGP was calculated by subtracting the systemic rate of appearance of the intraduodenally infused glucose from the total rate of appearance of glucose. Initial splanchnic glucose extraction was calculated as 1 minus the systemic rate of appearance of [3-3H]glucose divided by the intraduodenal infusion rate of [3-3H]glucose.

**Statistical analysis.** Data in the text and Figs. 1–3 are expressed as means ± SE. All rates are expressed as milligrams per kilogram total body weight per minute. ANOVA followed by a signed-rank test was used to compare the results of the different studies. A P value <0.05 was considered statistically significant.
RESULTS

Plasma glucose, insulin, C-peptide, and glucagon concentrations. Fasting plasma glucose concentrations (Fig. 1A) did not differ on the 0/0.1, 1.55, and 3.1 mg·kg⁻¹·min⁻¹ id study days (90 ± 1 vs. 90 ± 2 vs. 87 ± 1 mg/dl). Plasma glucose concentrations fell (P < 0.001) during the 7 h of study to 84 ± 2 mg/dl on the 0/0.1 mg·kg⁻¹·min⁻¹ id study day. In contrast, plasma glucose increased (P < 0.001) on both the 1.55 mg·kg⁻¹·min⁻¹ (to 104 ± 5 mg/dl) and 3.1 mg·kg⁻¹·min⁻¹ (to 107 ± 3 mg/dl) study days. Although slightly higher on the 3.1 mg·kg⁻¹·min⁻¹ study day, glucose concentrations did not differ significantly from those observed during the final hour of the 1.55 mg·kg⁻¹·min⁻¹ study days.

Fasting plasma insulin concentrations (Fig. 1B) did not differ on the 0/0.1, 1.55, and 3.1 mg·kg⁻¹·min⁻¹ id study days. Plasma glucose, insulin, C-peptide, and glucagon concentrations did not differ on the 0/0.1, 1.55, and 3.1 mg·kg⁻¹·min⁻¹ id study days. Plasma insulin concentrations did not differ by study end (7 ± 1 vs. 5 ± 1 μU/ml). Insulin concentrations fell during the 7 h of the 0/0.1 mg·kg⁻¹·min⁻¹ id study (to 3 ± 1 μU/ml). In contrast, insulin increased (P < 0.05) during the 1.55 and 3.1 mg·kg⁻¹·min⁻¹ infusions, reaching a peak of 10 ± 2 and 18 ± 5 μU/ml, respectively, by 2 h (P = 0.07; 1.55 vs. 3.1 mg·kg⁻¹·min⁻¹ infusions). Insulin concentrations then fell back to concentrations that no longer differed by study end (7 ± 1 vs. 8 ± 1 μU/ml). Of note, the plasma insulin concentrations of one individual were three SDs greater than those of the other subjects in that group both before and during the 1.55 mg·kg⁻¹·min⁻¹ infusion and therefore were excluded from analysis.

Fasting plasma C-peptide concentrations (Fig. 1C) also did not differ on the 0/0.1, 1.55, and 3.1 mg·kg⁻¹·min⁻¹ study days (0.4 ± 0.0 vs. 0.4 ± 0.1 vs. 0.3 ± 0.0 nmol/l). Plasma C-peptide concentrations fell (P < 0.001) to 0.3 ± 0 nmol/l during the 7 h of the 0/0.1 mg·kg⁻¹·min⁻¹ id study. In contrast, C-peptide increased (P < 0.01) during 3.1 mg·kg⁻¹·min⁻¹ id infusion to 0.8 ± 0.0 nmol/l. C-peptide tended to increase (to 0.8 ± 0.2 nmol/l) during the 1.55 mg·kg⁻¹·min⁻¹ id infusion. Plasma C-peptide concentrations did not differ (P = 0.5) during the final hour of the 1.55 and 3.1 mg·kg⁻¹·min⁻¹ id infusions (0.8 ± 0.2 and 0.8 ± 0.1 nmol/l).

Fasting plasma glucagon concentrations (Fig. 1D) did not differ on the 0/0.1, 1.55, and 3.1 mg·kg⁻¹·min⁻¹ id study days (134 ± 13 vs. 146 ± 8 vs. 115 ± 6 pg/ml). Glucagon concentrations fell (P < 0.01) during the 3.1 mg·kg⁻¹·min⁻¹ id infusion to 100 ± 6 ng/l and during the 1.55 mg·kg⁻¹·min⁻¹ id infusion to 128 ± 6 ng/l and remained unchanged during the 0/0.1 mg·kg⁻¹·min⁻¹ id infusion (125 ± 8). Growth hormone concentrations also did not differ on the three study days either before or during the intraduodenal infusions (data not shown).

Plasma [6,6-²H₂]glucose enrichment and [3-³H]glucose specific activity. Plasma [6,6-²H₂]glucose enrichment (Fig. 2A) remained essentially unchanged during the 7 h of the 0/0.1 mg·kg⁻¹·min⁻¹ id infusion. Plasma [6,6-²H₂]glucose enrichment fell during the first 2 h of the 1.55 and 3.1 mg·kg⁻¹·min⁻¹ id glucose infusions and changed minimally thereafter. The fall in plasma [6,6-²H₂]glucose enrichment was greater during the 3.1 than during the 1.55 mg·kg⁻¹·min⁻¹ id infusions, indicating a higher systemic rate of appearance of unlabeled glucose in the former.

The ratio of [6,6-²H₂]glucose to [³H]glucose fell during the first 3 h of the 0/0.1, 1.55, and 3.1 mg·kg⁻¹·min⁻¹ id infusions, indicating progressive absorption of the intraduodenally infused tracer (Fig. 2B). The ratio of [6,6-²H₂]glucose to [³H]glucose changed minimally thereafter.

Systemic rate of appearance of intraduodenally infused glucose, EGP, and glucose disappearance. The systemic rate of appearance of intraduodenally infused glucose increased during the first 3 h of the 1.55 and 3.1 mg·kg⁻¹·min⁻¹ id infusions, reaching a plateau thereafter (Fig. 3A). The appearance of intraduodenal...
glucose was greater ($P < 0.001$) during the final hour of the 3.1 than during the 1.55 mg·kg$^{-1}$·min$^{-1}$ id infusion ($3.66 \pm 0.2$ vs. $2.65 \pm 0.03$ mg·kg$^{-1}$·min$^{-1}$). No intraduodenal glucose appeared during 0/0.1 mg·kg$^{-1}$·min$^{-1}$ id infusions. Systemic appearance of intraduodenally infused tracer averaged $105 \pm 14, 108 \pm 3, and 113 \pm 18\%$ during the 0/0.1, 1.55, and 3.1 mg·kg$^{-1}$·min$^{-1}$ id infusions, respectively, indicating negligible splanchnic tracer extraction.

Fasting EGP (Fig. 3B) did not differ on the 0/0.1, 1.55, and 3.1 mg·kg$^{-1}$·min$^{-1}$ id study days ($2.34 \pm 0.1$ vs. $2.30 \pm 0.1$ vs. $2.35 \pm 0.1$ mg·kg$^{-1}$·min$^{-1}$). EGP suppressed to $1.98 \pm 0.2$ mg·kg$^{-1}$·min$^{-1}$ during the final hour of the 0/0.1 mg·kg$^{-1}$·min$^{-1}$ id infusion ($P < 0.05$); however, EGP suppressed to a greater degree during the final hour of the 1.55 and 3.1 mg·kg$^{-1}$·min$^{-1}$ id infusions to $0.84 \pm 0.1$ and $0.63 \pm 0.1$ mg·kg$^{-1}$·min$^{-1}$ ($P < 0.001$). However, EGP did not differ during the final hour of the 1.55 and 3.1 mg·kg$^{-1}$·min$^{-1}$ id infusions.

Fasting glucose disappearance (Fig. 3C) did not differ on the 0/0.1, 1.55, and 3.1 mg·kg$^{-1}$·min$^{-1}$ id study days ($2.32 \pm 0.3$ vs. $2.1 \pm 0.2$ vs. $2.3 \pm 0.2$ mg·kg$^{-1}$·min$^{-1}$). Glucose disappearance fell slightly, but not significantly, to $2.3 \pm 0.1$ during the 0/0.1 mg·kg$^{-1}$·min$^{-1}$ id infusions. Glucose disappearance during the final hour of the 1.55 and 3.1 mg·kg$^{-1}$·min$^{-1}$ id infusions ($4.47 \pm 0.2$ vs. $2.6 \pm 0.1$ vs. $2.3 \pm 0.1$ mg·kg$^{-1}$·min$^{-1}$) was greater ($P < 0.001$) than that observed over the same interval during the 0/0.1 mg·kg$^{-1}$·min$^{-1}$ id infusions. Glucose disappearance was higher ($P < 0.001$) during the final hour of the 3.1 mg·kg$^{-1}$·min$^{-1}$ id infusion than during the final hour of the 1.55 mg·kg$^{-1}$·min$^{-1}$ infusion.

**DISCUSSION**

Portal venous and arterial glucose concentrations do not differ in the fasting state, with both being lower than those in the hepatic vein (2, 15). Ingestion of a carbohydrate-containing meal results in a selective increase in the portal venous glucose concentration, thereby increasing the portal venous-to-hepatic venous glucose gradient (2, 15). This gradient is further accentuated by the increase in hepatic glucose uptake resulting from the accompanying postprandial increase in portal insulin concentrations (2, 3, 9–11, 18, 20, 23). Multiple studies have established that hepatic glucose uptake at any given insulin concentration is greater in the presence than in the absence of a portal venous-to-hepatic venous glucose gradient, implying the existence of so-called portal glucose “sensors” (2, 3, 9–11,
Studies in dogs have shown that activation of these receptors also results in a compensatory decrease in extrahepatic glucose uptake (3, 10). These experiments, however, employed relatively high portal venous glucose infusion rates to create gradients similar to those observed after food ingestion. Therefore, the reports by Burcelin et al. (5–7) that infusion of glucose in the portal vein of mice at rates approximating EGP caused marked hypoglycemia were surprising. The demonstration that this response did not occur when portal GLUT2 transporters were knocked out was particularly intriguing, since it implied that hypoglycemia was caused by selective activation of a portal venous glucose sensor (6).

The present experiments were undertaken to determine whether low rates of delivery of glucose in the portal vein also resulted in hypoglycemia. To do so, we infused glucose in the duodenum at rates of 1.55 and 3.1 mg·kg\(^{-1}\)·min\(^{-1}\). We chose these rates since we wanted to bracket the normal postabsorptive rate of EGP (i.e., ~2 mg·kg\(^{-1}\)·min\(^{-1}\)). Both infusions stimulated insulin secretion; however, in contrast to what was observed in mice (5–7), glucose concentrations rose rather than fell. The increase in glucose was evident whether considered as the change from the basal value or compared with the glucose concentrations observed over the same interval during the 0/0.1 mg·kg\(^{-1}\)·min\(^{-1}\) id glucose infusions. The rise in glucose concentration continued until glucose disappearance increased sufficiently to equal the sum of the systemic rate of appearance of the intraduodenally infused glucose and EGP. The increase in glucose and insulin concentrations during the 1.55 and 3.1 mg·kg\(^{-1}\)·min\(^{-1}\) infusions resulted in equivalent suppression of EGP. However, despite comparable glucose and insulin concentrations, glucose disappearance increased more during the 3.1 than during the 1.55 mg·kg\(^{-1}\)·min\(^{-1}\) id infusions, thereby compensating for the higher systemic rate of appearance of the intraduodenal glucose.

Thus selective intraportal infusion of glucose in humans did not cause hypoglycemia but may have enhanced glucose disposal.

It is interesting to speculate why glucose disappearance was higher during the 3.1 than during the 1.55 mg·kg\(^{-1}\)·min\(^{-1}\) id infusion. Burcelin et al. (6, 7) observed greater rates of glucose clearance during intraportal than during intravenous glucose infusion in mice. This effect did not occur in the GLUT2 knockout mice, suggesting a role for a portal glucose sensor (6). Activation of a portal glucose sensor that in turn enhanced extrahepatic glucose disposal also may have occurred in the present experiments. The higher rates of glucose disappearance during the 3.1 than during the 1.5 mg·kg\(^{-1}\)·min\(^{-1}\) id infusion despite comparable glucose, insulin, and C-peptide concentrations is consistent with this possibility. On the other hand, we have previously shown that glucose disappearance was the same when glucose was infused intraduodenally or intravenously in nondiabetic volunteers at a rate of 4.0 mg·kg\(^{-1}\)·min\(^{-1}\) (24). If the higher rates of glucose disappearance were mediated by a glucose sensor, this would imply a narrow dose-response curve, since this effect was absent during the current 1.55 and the past 4.0 mg·kg\(^{-1}\)·min\(^{-1}\) glucose id infusions but present during the current 3.1 mg·kg\(^{-1}\)·min\(^{-1}\) glucose infusions. On the other hand, glucose was clamped at ~150 mg/dl in our previous experiments, and somatostatin was infused to inhibit endogenous insulin secretion (24). Because somatostatin, perhaps by inhibiting GLP-1 secretion (12), blunts the “portal signal” in mice (5), our previous experiments could have missed a stimulatory effect of intraportal glucose delivery on glucose disappearance (24).

Alternatively, the higher rate of glucose disappearance during the 3.1 than during the 1.55 mg·kg\(^{-1}\)·min\(^{-1}\) id infusion could have been because of the residual effect of antecedent higher insulin concentration combined with the slightly (but not significantly) higher glucose concentration. As is evident from Fig. 1, both insulin and C-peptide concentrations tended to be higher during the 3.1 than during the 1.55 mg·kg\(^{-1}\)·min\(^{-1}\) id infusions, with the differences being most marked immediately after the start of the intraduodenal infusions. Glucose disappearance more closely reflects interstitial than plasma insulin concentrations, and a change in interstitial insulin concentration lags behind a change in plasma insulin concentration (25). Therefore, the higher plasma insulin concentrations during the first few hours of the 3.1 mg·kg\(^{-1}\)·min\(^{-1}\) id infusion could have resulted in higher rates of glucose disappearance several hours later. The present experiments therefore leave open the possibility that selective intraportal infusion at rates bracketing EGP may enhance extrahepatic glucose uptake in humans.

We infused glucose at rates of either 0 (i.e., saline alone) or 0.1 mg·kg\(^{-1}\)·min\(^{-1}\) as control experiments. We included these control experiments since we wanted to be able to determine whether a fall in glucose concentration (if observed) during the 1.55 and 3.1 mg·kg\(^{-1}\)·min\(^{-1}\) id glucose infusions was greater than that which occurred with fasting alone. We infused [3-H]glucose and carrier unlabeled glucose at a rate of 0.1 mg·kg\(^{-1}\)·min\(^{-1}\) in five of the subjects and [3-H]glucose with saline alone in four of the subjects. We included the saline-alone experiments since we were concerned that infusion of even a small amount of glucose in the duodenum might evoke an enteral signal, thereby obscuring differences that might occur with the higher intraduodenal glucose infusion rates. This was not the case since the results were the same during infusion of either the 0 (saline) or 0.1 mg·kg\(^{-1}\)·min\(^{-1}\) id infusions. Burcelin et al. (5) reported that the GLP-1 antagonist exendin-(9–36) prevented hypoglycemia during intraportal glucose infusion in mice, whereas GLP-1 infusion did not. This suggested that the presence of basal levels of GLP-1 acting alone or in combination with other incretin hormones is required for activation of the portal signal in mice. We presume that incretin levels either remained constant or increased slightly during the intraduodenal glucose infusions. Therefore, the lack of
hypothesis in humans that enhances extrahepatic glucose with, but does not prove the existence of, a portal higher glucose and insulin concentrations is consistent infusion in the presence of slightly but not signiﬁcant decrease in arterial-portal glucose gradient decreases skeletal muscle glucose uptake. Am J Physiol Endocrinol Metab 275: E101–E111, 1998.


DISCLOSURES

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