Effects of Glucagon on Postprandial Carbohydrate Metabolism in Nondiabetic Humans

J.W. Frank, M. Camilleri, G.M. Thomforde, S.F. Dinneen, and R.A. Rizza

The present experiments sought to determine whether glucagon concentrations mimicking those observed in people with diabetes mellitus alter postprandial carbohydrate metabolism in nondiabetic humans. We measured the gastric emptying of solids and liquids, the systemic rate of appearance of ingested glucose, and endogenous glucose production either when postprandial suppression of glucagon was prevented by infusing glucagon at a rate of 0.65 ng/kg/min, when postprandial glucagon concentrations were elevated by infusing glucagon at a rate of 3.0 ng/kg/min, or when postprandial suppression of glucagon was permitted by infusion of saline. Despite marked differences in glucagon concentrations, postprandial glucose and insulin concentrations did not differ on any occasion. Although gastric emptying of liquids and solids was comparable on all three occasions, the high-dose, but not the low-dose, glucagon infusion caused a slight delay in the systemic appearance of ingested glucose and a significant decrease ($P < .01$) in postprandial D-xylose concentrations, suggesting a delay in carbohydrate absorption. However, this was offset by an increase ($P < .05$) in endogenous glucose production, resulting in no difference in postprandial glucose appearance. We conclude that in the absence of insulin deficiency, neither a lack of suppression of glucagon nor an elevation of glucagon to levels encountered in uncontrolled diabetes mellitus cause postprandial hyperglycemia in nondiabetic humans.

THE IMPORTANCE OF GLUCAGON in the regulation of endogenous glucose production in nondiabetic humans in the postabsorptive state (ie, when insulin concentrations are low) is well established. Glucose production increases when glucagon increases and decreases when glucagon decreases, with the effects being most evident in the presence of changing rather than constant glucagon concentrations.[1-6] The role of glucagon in the regulation of endogenous glucose production in the postprandial state (ie, when insulin concentrations are high) in nondiabetic humans is less well established. This uncertainty likely results from the fact that although glucagon is a potent stimulator of glycogenolysis and gluconeogenesis, this action is opposed by a concurrent increase in insulin.[7] Liljenquist and Rabin[8] have previously reported that infusion of glucagon does not alter glucose concentrations following a glucose tolerance test in nondiabetic volunteers. However, since these studies only measured the glucose concentration, they did not permit direct evaluation of the effects of glucagon on postprandial hepatic production; a glucagon-induced delay in gastric emptying[9-14] and/or decrease in splanchnic glucose uptake[7] could have offset any effect of glucagon on glucose output. In contrast, Taylor et al,[15] using a dual-isotope method to directly measure glucose output, have recently reported that changes in endogenous glucose production following a mixed meal closely parallel changes in the plasma glucagon to insulin ratio. Although this observation suggests a regulatory role for glucagon, it does not prove it, since concurrent (and reciprocal) changes in insulin may have been the dominant factor.

The present experiments therefore sought to determine whether changes in glucagon per se alter postprandial carbohydrate metabolism in nondiabetic humans. Subjects were studied in three experimental conditions: when postprandial suppression of glucagon was either prevented by infusing glucagon at a rate of 0.65 ng/kg/min, when the postprandial glucagon concentration was elevated by infusing glucagon at a rate of 3.0 ng/kg/min, or when postprandial suppression of glucagon was permitted by infusion of saline. We report that the high-rate, but not the low-rate, glucagon infusion increased postprandial endogenous glucose production. However, these effects were offset by a glucagon-induced delay in carbohydrate absorption, resulting in no change in postprandial glucose concentrations. Thus, even marked elevations in glucagon have minimal effects on postprandial carbohydrate metabolism in nondiabetic humans. These results provide further experimental support for the conclusion that insulin, not glucagon, is the dominant regulator of postprandial endogenous glucose release in nondiabetic humans.

SUBJECTS AND METHODS

Subjects

Following study approval by the Mayo Institutional Review Board, 12 healthy white volunteers provided informed written consent to participate in the experiments. All subjects were studied twice. On one occasion, subjects were infused with saline. On the other occasion, they received either a low-dose (0.65 ng/kg/min) or high-dose (3 ng/kg/min) glucagon infusion (n = 6 each). The age (56 ± 3 *v* 61 ± 4 years), body mass index (26.8 ± 2.3 *v* 29.1 ± 0.8 kg/m^2), and gender (two males and four females *v* four males and two females) did not differ significantly between groups. Results observed during the saline infusions have been previously reported as part of a study examining the effects of non–insulin-dependent diabetes mellitus on gastric function.[16] All subjects had normal fasting glucose and normal glycosylated hemoglobin concentrations. Volunteers were excluded if they had dysautonomic or gastrointestinal symptoms, gastrointestinal disease, or abdominal surgery, with the exception of uncomplicated appendectomy, herniorrhaphy, or gynecological surgery as determined by interview and by review of medical records.

Protocol

The subjects were admitted to the General Clinical Research Center on the afternoon before study to assess autonomic function as previ-

From the Gastroenterology and Endocrine Research Units, Mayo Clinic and Mayo Foundation, Rochester, MN.

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Address reprint requests to R.A. Rizza, MD, Endocrine Research Unit, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

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ously described.[16] Pregnancy was excluded in menstruating women by measuring the serum level of β-human chorionic gonadotropin. Subjects ingested a standardized meal (570 kcal, 21% protein, 48% carbohydrate, and 30% fat) at 5:00 to 5:30 PM on the evening before study. Subjects were permitted to consume noncaffeinated, noncaloric beverages until midnight, after which they received nothing by mouth.

Subjects were awakened at 6:00 AM on the day of study, and two intravenous catheters were inserted. One was placed in a retrograde fashion into a vein of the right hand, which was kept in a heated (55° to 60°C) plexiglas box to permit sampling of arterialized blood. The other was inserted into a vein of the contralateral forearm and used for tracer, glucagon, or saline infusion. A primed (~12 μCi), continuous (~0.12 μCi/min) intravenous infusion of [6-^{3}H]glucose was started at 7:00 AM to permit measurement of glucose turnover. At 10:00 AM, having allowed 3 hours for isotopic equilibration, all subjects ingested a standard breakfast containing three chicken eggs and 50 g dextrose mixed in 200 mL sugar-free jello (446 kcal, 16% protein, 48% carbohydrate, and 36% fat). The eggs were mixed with 0.1 mCi ^{111}In-labeled ion-exchange pellets (mean diameter, 1 mm; Amberlite 120-IR-Plus; Sigma Chemical, St Louis, MO) and scrambled to a firm consistency.[16] The dextrose was mixed with 100 μCi [2-^{3}H]glucose before being added to the jello. Once jelled, 10 0.1-mL aliquots of ^{99m}Tc (1 mCi) were injected into the jello. Ten grams of D-xylose in 100 mL water and 150 mL additional water were served with the meal. All fluids, including the jello, were served at room temperature. First, the jello and D-xylose were consumed within a period of 2 minutes and a gamma camera scan was obtained. The eggs and water were then eaten within a period of 5 minutes.

Infusions of glucagon or saline also were started at 10:00 AM and continued until 12:00 noon. Glucagon was infused at a rate of either 0.65 or 3.0 ng/kg/min. Both the order of study and the dose of glucagon were determined at random. Studies in the same patient were separated by at least 1 week. Arterialized samples were drawn at regular intervals before and after meal ingestion for hormone and substrate measurement. Blood samples were placed on ice, centrifuged at 4°C, and stored at −20°C.

Measurement of Gastric Emptying

Gastric emptying was measured scintigraphically[16,17] using anterior and posterior large-field-of-view gamma cameras, each with a medium-energy, parallel-hole collimator (GE Starcam and Starport; General Electric, Milwaukee, WI). With the patient seated at an angle of 45° to the horizontal, static images were acquired for 2 minutes at 5-minute intervals for the first hour, 15-minute intervals for the second and third postprandial hours, and 1-hour intervals for the remaining 3 hours.

Gastric emptying was analyzed by drawing regions of interest around the gastric outline and determining the percentage of radioactivity remaining in the stomach at each time point. After correcting for downscatter from the ^{111}In (247 keV ± 10%) to the ^{99m}Tc (140 keV ± 10%) window and for isotope decay, the counts were plotted and the points from time zero to the time at which 10% or less of the initial radioactivity remained in the stomach were analyzed by the power exponential model using the NLIN procedure in the SAS software package[18] as previously described.[16,17] The equation was $prop_t = a_o \times [-kt]\beta$, where $prop_t$ is the proportion of counts at time t, a_o is the original proportion in the region of interest at time zero, k is the emptying rate constant, and β describes the initial shape of the gastric emptying curve. Results of gastric emptying are thus expressed as kappa (κ) values, where larger numbers correspond to more rapid emptying, and beta (β) values, where a number greater than 1 indicates the initial retention of isotope before emptying begins (ie, a lag period) and a value less than 1 indicates no lag period.

Analytical Methods

[2-^{3}H]glucose and [6-^{3}H]glucose specific activities were measured by selective enzymatic detritiation as previously described.[19] The glucose concentration was measured using a glucose oxidase method (Yellow Springs Instruments, Yellow Springs, OH). Glucagon, insulin, C-peptide, cholecystokinin (CCK), glucose-dependent insulinotropic polypeptide (GIP), neurotensin, and peptide YY (PYY) levels were measured by radioimmunoassay.[20-23] All antibody specificities have been previously characterized with less than 1% cross-reactivity with other peptides, except for the CCK antibody, which is directed at CCK-8 but cross-reacts[20] with CCK-33 (60%) and sulfated gastrin (10%).

Calculation of Glucose Turnover

Rates of glucose appearance and disappearance were calculated using Steele's non–steady-state equations.[24] The volume of distribution of glucose was assumed to equal 200 mL/kg, and the pool correction factor was assumed to equal 0.65. The intravenously infused [6-^{3}H]glucose was used to trace the rate of appearance of labeled and unlabeled ingested glucose as previously described.[21,25,26] The rate of endogenous glucose production was calculated as the difference between total glucose appearance and the rate of appearance of ingested glucose.[21,25,26]

Statistical Analysis

All data in the text and figures are presented as the mean ± SEM. Basal values were calculated by determining mean values for the data present from −30 to 0 minutes. Integrated responses above and below basal were calculated using the trapezoidal rule. Two-tailed paired Student's *t* tests were used to test the hypothesis that the results observed during glucagon infusion differed from those observed during saline. A *P* value less than .05 was considered statistically significant.

RESULTS

Plasma Glucose, Insulin, C-Peptide, and Glucagon Concentrations

Plasma glucose concentrations during the 0.65- and 3.0-ng/kg/min glucagon infusions did not differ from those observed during the saline infusions either before or after meal ingestion (Fig 1). Both preprandial (44 ± 4 *v* 42 ± 5 and 41 ± 6 *v* 46 ± 7 pmol/L) and integrated postprandial insulin responses above basal (Fig 1) during the 0.65-mg/kg/min (46 ± 8 *v* 38 ± 4 nmol/L, $P = .5$) and 3.0-ng/kg/min (36 ± 11 *v* 39 ± 12 nmol/L, $P = .5$) glucagon infusions were comparable to those observed during the respective saline infusion. C-peptide concentrations observed before glucagon and saline infusions, respectively, did not differ on either the 0.65-ng/kg/min (0.52 ± 0.07 *v* 0.45 ± 0.7) or 3.0-ng/kg/min (0.54 ± 0.08 *v* 0.61 ± 0.08 nmol/L) study days. Similarly, the integrated postprandial C-peptide responses above basal during glucagon and saline infusions, respectively, also did not differ during the 0.65-ng/kg/min (495 ± 87 *v* 545 ± 51 nmol/L, $P = .30$) or 3.0-ng/kg/min (392 ± 93 *v* 522 ± 130 nmol/L, $P = .15$) glucagon infusions. In contrast, whereas plasma glucagon decreased following meal ingestion during saline infusions, glucagon increased to a peak of 133 ± 9 and 390 ± 84 pg/mL during the 0.65- and 3.0-ng/kg/min glucagon infusions (Fig 1). This resulted in higher ($P < .01$) glucagon concentrations for the first 2 hours after meal ingestion during both glucagon infusions versus the saline infusions.

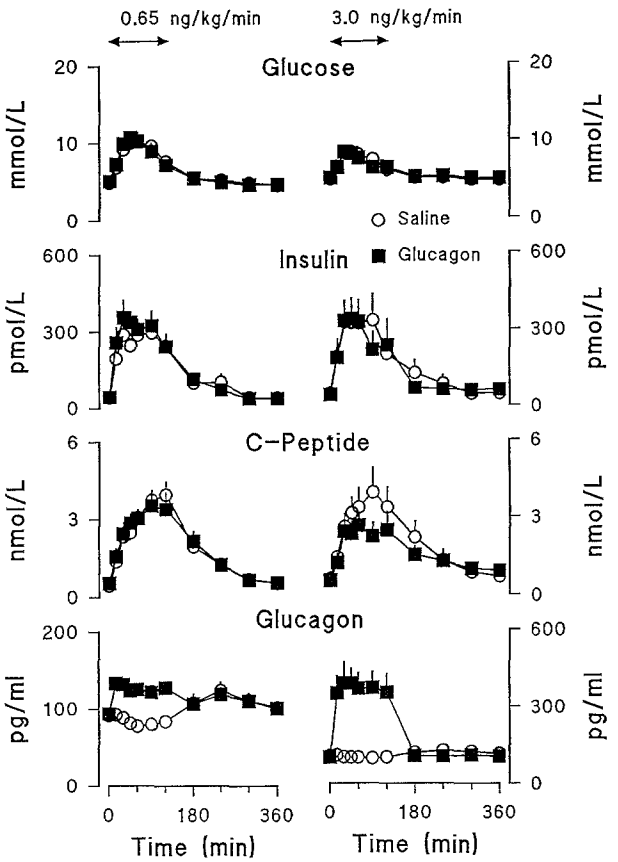

Fig 1. Plasma glucose, insulin, C-peptide, and glucagon following ingestion of a mixed meal at time zero. Saline or glucagon was infused from 0 to 120 minutes. Glucagon was infused at a rate of either 0.65 ng/kg/min (left panels) or 3.0 ng/kg/min (right panels). Note differences in scale for glucagon concentrations between left and right panels.

Glucose Appearance and Disappearance

Glucose appearance and disappearance (Fig 2) did not differ during the glucagon infusions versus the saline infusion either before or after meal ingestion.

Gastric Emptying and Meal Glucose Appearance

For ingested carbohydrate to reach the systemic circulation and therefore contribute to glucose appearance, it must pass through several steps. First, it must be emptied from the stomach. Next, it must transverse the absorptive surfaces of the gut. Finally, it must pass through the liver, where a portion may be retained to replenish hepatic glycogen, with the rest being permitted to enter the systemic circulation. The effects of glucagon on each of these steps were examined.

Gastric emptying of both liquids and solids was similar during the initial 2 hours following meal ingestion on all study days (Fig 3). The high-dose glucagon infusion resulted in a slight but statistically nonsignificant delay in emptying solids during the last 2 hours of the experiment. Plasma D-xylose concentrations following meal ingestion were slightly but significantly ($P < .01$) lower during the 3.0-ng/kg/min glucagon infusion versus the saline infusion (Fig 4), implying decreased carbohydrate absorption. On the other hand, while the systemic rate of appearance of ingested glucose also was slightly lower during the first 2 hours of high-dose glucagon versus saline infusion (1,047 ± 193 *v* 1,457 ± 220 μmol/kg/6 h, $P = .17$), these differences did not reach statistical significance. Neither the plasma D-xylose concentration nor the systemic rate of appearance of ingested glucose differed during the 0.65-ng/kg/min glucagon infusion versus saline infusion (Fig 4).

Endogenous Glucose Production

Endogenous glucose production (Fig 5) was comparably suppressed following meal ingestion during the 0.65-ng/kg/min glucagon and saline infusions (−516 ± 40 *v* −473 ± 60 μmol/kg/2 h). In contrast, the 3.0-ng/kg/min glucagon infusion led to less ($P < .05$) suppression of endogenous glucose production than the saline infusion (−193 ± 90 *v* −473 ± 60 μmol/kg/2 h) during the first 2 hours following meal ingestion, with rates converging thereafter.

Gastrointestinal Hormones

CCK, GIP, neurotensin, and PYY concentrations were comparable before and after meal ingestion on all study days (data not shown).

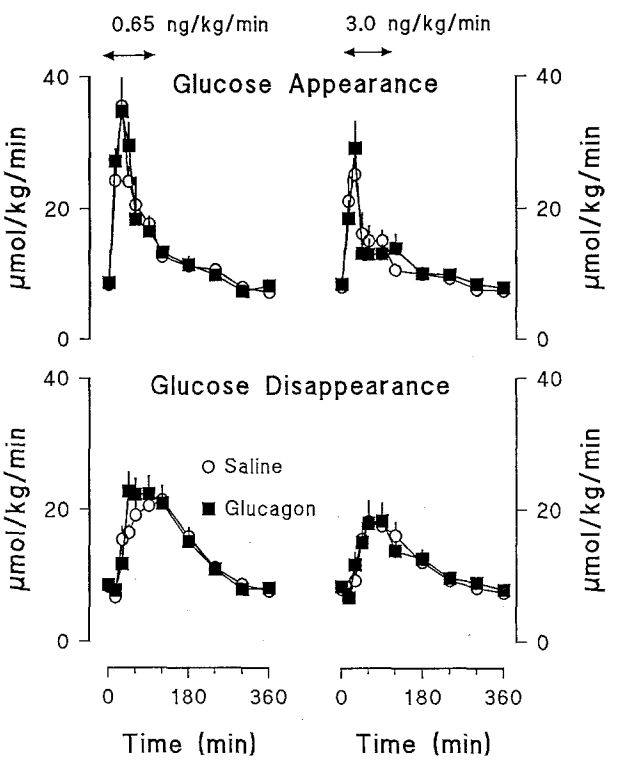

Fig 2. Rates of glucose appearance (equal to the sum of endogenous glucose production and rate of appearance of ingested glucose) and disappearance following ingestion of a mixed meal at time zero. Saline or glucagon was infused from 0 to 120 minutes. Glucagon was infused at a rate of either 0.65 ng/kg/min (left panels) or 3.0 ng/kg/min (right panels).

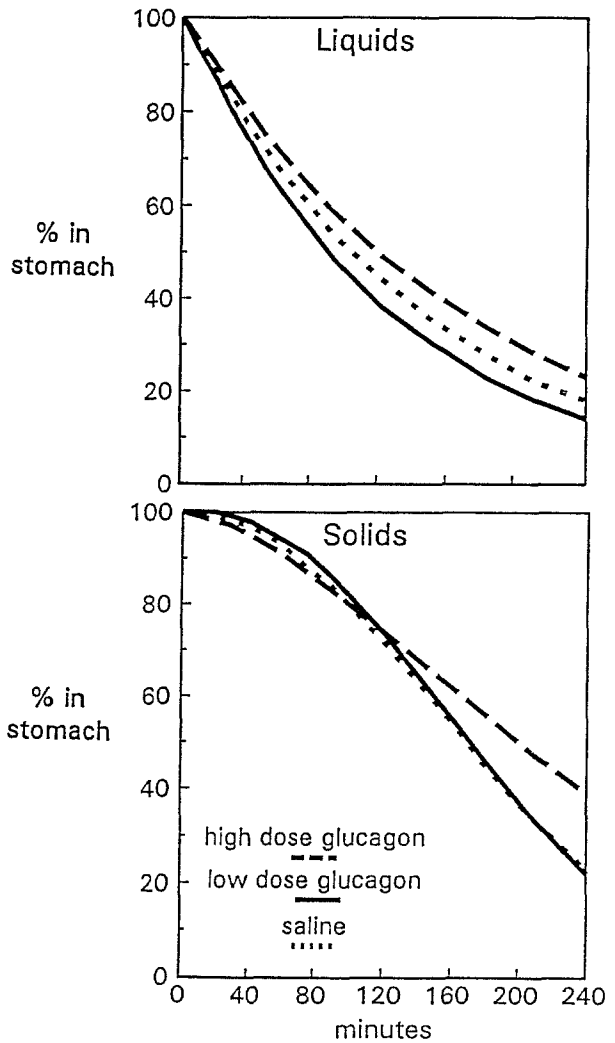

Fig 3. Effects of infusion of saline or glucagon at a rate of either 0.65 ng/kg/min (low-dose glucagon) or 3.0 ng/kg/min (high-dose glucagon) from 0 to 120 minutes on gastric emptying of liquids and solids following ingestion of a mixed meal at time zero.

DISCUSSION

In the postabsorptive state, infusion of glucagon results in a prompt increase in both endogenous glucose production and glucose concentration.[1-6] The magnitude of stimulation and the resultant increase in glucose concentration increases with increasing glucagon concentration. In contrast, the present experiments indicate that in the fed state, glucagon has a minimal, if any, effect on either of these variables in nondiabetic humans. These results differ from our previous findings in subjects with insulin-dependent diabetes. In those experiments, infusion of glucagon at a rate of 0.65 ng/kg/min following ingestion of the same mixed meal resulted in substantial stimulation of endogenous glucose production and a 40- to 50-mg/dL increment in plasma glucose concentrations.[26] The primary difference between the two experiments likely lies in the fact that the diabetic subjects in the previous studies were relatively insulin-deficient and the nondiabetic subjects in the present studies were not. Perhaps even more surprising, al-

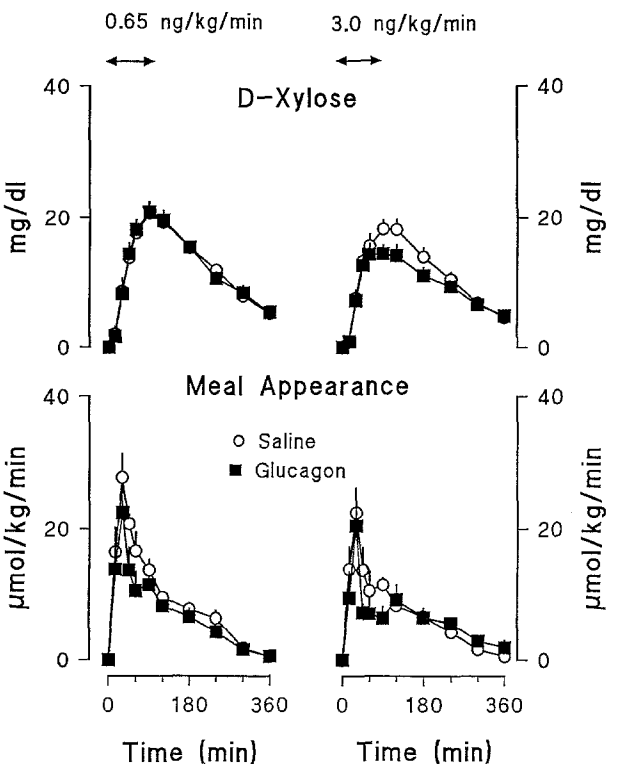

Fig 4. Plasma D-xylose concentration and systemic rate of appearance of ingested glucose following ingestion of a mixed meal at time zero. Saline or glucagon was infused from 0 to 120 minutes. Glucagon was infused at a rate of either 0.65 ng/kg/min (left panels) or 3.0 ng/kg/min (right panels).

though the high-dose glucagon infusion in the present studies resulted in an increase in circulating glucagon to 300 to 400 pg/mL, it had only a minimal effect on postprandial endogenous glucose production in the present studies. This effect was transient (Fig 5) and was offset by a decrease in the rate of meal appearance over the same interval (Fig 4). Although the

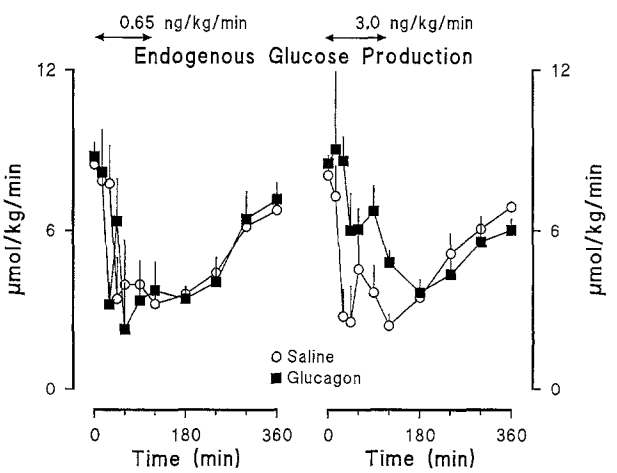

Fig 5. Rate of endogenous glucose production following ingestion of a mixed meal at time zero. Saline or glucagon was infused from 0 to 120 minutes. Glucagon was infused at a rate of either 0.65 ng/kg/min (left panels) or 3.0 ng/kg/min (right panels).

decrease in meal appearance was not statistically significant, the magnitude of the decrease (~400 μmol/kg) was equal to the increase in endogenous glucose production, thereby accounting for the fact that the integrated glycemic response did not differ over the 6 hours of study. The current experiments are consistent with the previous report by Liljenquist and Rabin[8] that a 3-ng/kg/min glucagon infusion did not alter glucose concentrations following an approximately 70-g glucose load. Taken together, these studies strongly suggest that the rapid increase in insulin that occurs in nondiabetic subjects following food ingestion effectively limits the ability of glucagon to stimulate endogenous glucose production. Thus, relative or absolute insulin deficiency such as occurs with diabetes mellitus appears to be necessary for the failure of postprandial glucagon suppression to cause a deterioration in glucose tolerance.

The present experiments used the dual-isotope method to distinguish glucose derived from the meal from glucose released by the liver.[21,25,26] A decrease in meal glucose appearance could result from a decrease in intestinal absorption, an increase in splanchnic glucose uptake, or a combination of both. D-Xylose was included in the meal in an effort to gain insight as to whether glucagon alters these processes. D-Xylose is absorbed by passive diffusion and is not further metabolized by the liver.[27,28] In contrast, glucose is absorbed via sodium-dependent glucose transporters.[28] Thus, D-xylose provides a qualitative rather than quantitative measure of monosaccharide glucose absorption. The lower plasma D-xylose concentrations during the 3.0-ng/kg/min glucagon infusion are suggestive of an impairment in absorption. Although very high doses of glucagon can decrease intestinal motility,[9-14] this is unlikely to be the cause of the lower D-xylose concentrations, since neither the 0.65-ng/kg/min nor the 3.0-ng/kg/min glucagon infusion altered gastric emptying. This conclusion is further supported by the fact that concentrations of CCK, GIP, neurotensin, and PYY did not differ during the glucagon and saline infusions, because secretion of these hormones is a function of the rate of nutrient delivery to the small intestine. In any case, the effects of glucagon on glucose absorption obviously were small, since they were not sufficient to alter either the rate or the proportion of ingested glucose that eventually reached the systemic circulation.

As with all experiments, the present studies suffer from some limitations. Peripheral rather than portal glucagon concentrations were measured. Although we do not know the exact portal glucagon concentrations present on each occasion, concentrations were obviously higher during glucagon versus saline infusion and during high-rate versus low-rate glucagon infusion. Similarly, we did not measure portal insulin concentrations. However, C-peptide concentrations, if anything, tended to be slightly (but not significantly) lower during glucagon versus saline infusion, arguing against a compensatory increase in portal insulin concentrations. Although glucagon is a known insulin secretagogue,[29] the comparable C-peptide concentrations during saline and glucagon infusions implies that the increase in glucose and other incretins following ingestion of the mixed meal was the primary stimuli of insulin secretion. Glucagon is most potent when administered as a pulsatile infusion.[30] The low-dose (ie, 0.65 ng/kg/min) glucagon infusion was chosen in an effort to prevent a decrease in calculated postprandial portal venous glucagon concentrations.[26] This approach resulted in relatively small differences in glucagon concentrations on glucagon and saline infusion days. Therefore, we may have missed a subtle effect that would have been more evident if the 0.65-ng/kg/min glucagon infusion had been administered in a pulsatile manner. However, we doubt if the pattern of administration can account for the total lack of effect of the 3.0-ng/kg/min glucagon infusion on meal glucose tolerance, since numerous studies have demonstrated that this infusion rate in the postabsorptive state results in marked stimulation of hepatic glucose production and a substantial increase in plasma glucose.[1-6]

When studying a small number of subjects, it is always possible that an effect was present but not detected. Although there was considerable variability in endogenous glucose production during the 0.65-mg/kg/min infusion, this was primarily due to intersubject rather than intrasubject variability. Of note, postprandial suppression of endogenous glucose production was numerically greater in five of six subjects during saline infusion versus the 0.65-ng/kg/min glucagon infusion. Therefore, there was no hint that we missed a stimulatory effect of glucagon. Similarly, there was no suggestion that either the 0.65-ng/kg/min or 3.0-ng/kg/min glucagon infusions caused postprandial hyperglycemia, since the integrated glycemic responses were lower (rather than higher) in four of six subjects during the glucagon versus saline infusion. Finally, we have only examined the effects of two glucagon infusion rates. The lower rate was chosen because it prevented the normal postprandial decrease in plasma glucagon,[31] whereas the higher rate resulted in plasma concentrations mimicking the levels observed in severe stress.[32-34] We therefore cannot exclude the possibility that still higher concentrations of glucagon can alter postprandial glucose concentrations in nondiabetic individuals. Finally, we have only examined the effects of glucagon on postprandial glucose metabolism. The extent to which increases in glucagon alter postprandial fat and amino acid metabolism remains to be determined.

In summary, (1) the 3.0-ng/kg/min but not the 0.65-mg/kg/min glucagon infusion increased postprandial endogenous glucose production, but these effects were offset by a glucagon-induced delay in carbohydrate absorption, resulting in no change in postprandial glucose concentrations; (2) physiologic glucagon concentrations do not alter either gastric emptying or systemic glucose disappearance; (3) a lack of postprandial suppression of glucagon does not cause hyperglycemia in nondiabetic humans; and (4) marked elevations in glucagon have minimal effects on postprandial carbohydrate metabolism. Taken in conjunction with previous studies in insulin-deficient diabetic humans,[26] the present results provide further experimental support for the conclusion that insulin, not glucagon, is the dominant regulator of postprandial carbohydrate metabolism.

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