

Lack of Suppression of Glucagon Contributes to Postprandial Hyperglycemia in Subjects with Type 2 Diabetes Mellitus*

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ABSTRACT

We tested the hypothesis that a lack of suppression of glucagon causes postprandial hyperglycemia in subjects with type 2 diabetes. Nine diabetic subjects ingested 50 g glucose on two occasions. On both occasions, somatostatin was infused at a rate of 4.3 nmol/kg·min, and insulin was infused in a diabetic insulin profile. On one occasion, glucagon was also infused at a rate of 1.25 ng/kg·min to maintain portal glucagon concentrations constant (nonsuppressed study day). On the other occasion, glucagon infusion was delayed by 2 h to create a transient decrease in glucagon (suppressed study day). Glucagon concentrations on the suppressed study day fell to about 70 ng/L during the first 2 h, rising thereafter to approximately 120 ng/L. In contrast, glucagon concentrations on the nonsuppressed study day remained constant at about 120 ng/L throughout. The decrease in

glucagon resulted in substantially lower ($P < 0.001$) glucose concentrations on the suppressed compared with the nonsuppressed study days (9.2 ± 0.7 vs. 10.9 ± 0.8 mmol/L) and a lower ($P < 0.001$) rate of release of [^{14}C]glucose from glycogen (labeled by infusing [$1\text{-}^{14}\text{C}$]galactose). On the other hand, flux through the hepatic UDP-glucose pool (and, by implication, glycogen synthesis), measured using the acetaminophen glucuronide method, did not differ on the two occasions. We conclude that lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes at least in part by accelerating glycogenolysis. These data suggest that agents that antagonize glucagon action or secretion are likely to be of value in the treatment of patients with type 2 diabetes. (*J Clin Endocrinol Metab* 85: 4053–4059, 2000)

SUBJECTS WITH TYPE 2 diabetes have either normal or slightly elevated fasting glucagon concentrations that fail to decrease appropriately after food ingestion (1–9). We previously demonstrated that a lack of suppression of glucagon causes marked hyperglycemia when insulin secretion is impaired, but minimally alters glucose tolerance when insulin secretion is intact (10–12). However, those experiments were carried out in lean nondiabetic and type 1 diabetic subjects (10–12). The applicability of these studies to people with type 2 diabetes is not known. Type 2 diabetes is characterized by alterations in both insulin secretion and insulin action (13–18). As the severity of these defects increases, the ability of glucose to stimulate its own uptake and to suppress its own release becomes a progressively more important determinant of glucose tolerance (19–25). Under these circumstances, suppression of glucagon may become moot, as glucagon appears to act primarily by opposing the effects of insulin (26–29). If so, glucagon antagonists will probably have a limited role in the treatment of type 2 diabetes. On the other hand, by lowering the hepatic sinusoidal glucagon to insulin ratio, suppression of glucagon may improve hepatic insulin action and thereby restore the normal

synergistic effects of insulin and hyperglycemia on the regulation of hepatic glucose metabolism.

The present experiments were undertaken to distinguish between these two possibilities. Nine subjects with type 2 diabetes were studied on two occasions. On each occasion, the subjects ingested 50 g glucose. A low dose of somatostatin was infused on both occasions to inhibit glucagon and insulin secretion. Identical amounts of insulin were infused in a pattern that created a typical postprandial diabetic insulin profile to insure that insulin concentrations were equal on both occasions. On one occasion glucagon was infused at a constant rate throughout the experiment, whereas on the other occasion the glucagon infusion was delayed for 2 h, thereby creating a transient decrease in plasma glucagon immediately following glucose ingestion, mimicking the pattern normally observed in nondiabetic subjects. Acetaminophen was given by mouth, and [$1\text{-}^{14}\text{C}$]galactose was infused iv to determine whether lack of suppression of glucagon decreases UDP-glucose flux (an indicator of glycogen synthesis) and/or increases the release of [^{14}C]glucose from glycogen (an indicator of glycogenolysis).

Subjects and Methods

Subjects

After approval from the Mayo Clinic institutional review board, nine subjects with type 2 diabetes mellitus gave written consent to participate in the study. The subjects were 55 ± 8 yr of age, had a body mass index of 30 ± 1 kg/m², and had had diabetes for an average of 5 ± 2 yr. Two of the nine volunteers were women, and seven were men. All subjects were in good health, had normal blood pressure, and were at a stable weight. None regularly engaged in vigorous exercise. At the time of screening, four subjects were being treated with diet alone, and five were

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being treated with a sulfonyleurea or metformin. None was taking a thiazolidine-dione. Antihyperglycemic agents were stopped at least 3 weeks before the study. Fasting glucose concentrations averaged 8.9 ± 1.1 mmol/L after withdrawal of the antihyperglycemic agents. Subjects were taking no medications other than oral contraceptive pills, estrogen, or T_4 replacement at the time of study.

Experimental design

All subjects were studied on two occasions, separated by at least 5 days. Subjects were admitted to the General Clinical Research Center at 1700 h on the evening before each study. After the ingestion of a standard 10 Cal/kg meal (50% carbohydrate, 15% protein, and 35% fat) between 1730–1800 h, subjects fasted (with the exception of occasional sips of water) until the following morning. After the evening meal, an 18-gauge catheter was inserted into a forearm vein, and insulin infusion was started (100 U regular human insulin in 1 L 0.9% saline containing 5 mL 25% human albumin) (30) to maintain plasma glucose concentrations at about 5 mmol during the night. Another cannula was inserted retrogradely into a dorsal vein of the other hand on the morning of the study. This hand was then placed in a heated Plexiglas box and maintained at a temperature of approximately 55 C to allow sampling of arterialized venous blood.

At 1000 h (0 min), the subjects drank an orange-flavored carbonated 50-g glucose drink (Sun-Dex 50, CMS/Fisher Healthcare, Houston, TX) over less than 5 min. A somatostatin (Bachem, Torrance, CA) infusion (4.3 nmol/kg·min) was started at 1000 h to inhibit endogenous glucagon secretion. GH (Genentech, Inc., South San Francisco, CA) also was infused at a rate of 3.0 ng/kg·min to maintain constant basal levels. A variable infusion of insulin designed to mimic a typical diabetic postprandial insulin profile was started at 1000 h to insure that insulin concentrations were equal on both occasions (13). On one occasion a glucagon (Eli Lilly & Co., Indianapolis, IN) infusion (1.25 ng/kg·min) was started at 1000 h and continued throughout the study in an effort to maintain portal venous glucagon concentrations constant. On the other occasion, the glucagon infusion (1.25 ng/kg·min) was not started until 1200 h, thereby permitting glucagon to fall during the first 2 h, as normally occurs in nondiabetic individuals after carbohydrate ingestion (2, 5, 26, 31). The order of study was random.

A constant infusion of $[1-^{14}\text{C}]$ galactose (0.15 $\mu\text{Ci}/\text{min}$; New England Nuclear Corp., Boston, MA) was initiated at 1000 h and continued until the end of the study. Subjects also ingested 2 g acetaminophen (pediatric suspension; 2 g/20 mL) at 1000 h. Subjects were asked to void urine at 1000 h and again at the end of the study. Urine was collected for the measurement of acetaminophen $[^{14}\text{C}]$ glucuronide specific activity to measure flux through the hepatic UDP-glucose pool (32). A primed (33 $\mu\text{mol}/\text{kg}$) continuous (0.33 $\mu\text{mol}/\text{kg}\cdot\text{min}$) infusion of $[6,6-^2\text{H}_2]$ glucose was started at 0600 h to trace the appearance of unlabeled glucose and $[^{14}\text{C}]$ glucose. Beginning at 1000 h, the infusion rate of $[6,6-^2\text{H}_2]$ glucose was varied so as to approximate the pattern of change in glucose appearance that was anticipated after glucose ingestion. To do so, the infusion rate of $[6,6-^2\text{H}_2]$ glucose was maintained at 100% from –240 to 0 min, at 150% from 1–15 min, at 400% from 16–30 min, at 300% from 31–45 min, at 200% from 46–60 min, at 125% from 61–90 min, and at 100% from 91 min to the end of the study. This resulted in maintenance of plasma glucose molar percent enrichment within 20% of the basal level on all study days. As the hyperglycemia and hyperinsulinemia that occur after glucose ingestion result in a net flux of glucose into glycogen via the hepatic UDP-glucose, and as iv infused $[1-^{14}\text{C}]$ galactose directly enters the hepatic UDP-glucose pool, the rate of release of $[^{14}\text{C}]$ glucose from glycogen into the systemic circulation provides an index of the rate of glycogenolysis (32–36).

Arterialized venous blood was collected at regular intervals for measurement of glucose and hormone concentrations as well as $[^{14}\text{C}]$ glucose specific activity and $[6,6-^2\text{H}_2]$ glucose molar enrichment.

Analytical techniques

Arterialized plasma samples were placed on ice, centrifuged at 4 C, separated, and stored at –20 C until assay. Plasma C peptide and glucagon concentrations were measured by RIA using reagents purchased from Linco Research, Inc. (St. Louis, MO). Plasma insulin and GH concentrations were measured using a double antibody chemilumines-

cence method with the Access immunoassay system (Beckman Coulter, Inc., Chaska, MN). Plasma $[^{14}\text{C}]$ glucose specific activity (37) and $[6,6-^2\text{H}_2]$ glucose molar enrichment (38) were determined as previously described. Body composition was measured by dual energy x-ray absorptiometry (DEXA scanner, Hologic, Inc., Waltham, MA). Glucose and lactate concentrations were measured using a glucose and lactate analyzer (YSI, Inc. <zcomx<, Yellow Springs, OH).

Calculations

The molar percent enrichment of $[6,6-^2\text{H}_2]$ glucose was smoothed using the OOPSEG program developed by Bradley *et al.* (39). The rate of appearance of unlabeled glucose was calculated using the nonsteady state equations of Steele *et al.* (40) and $[6,6-^2\text{H}_2]$ glucose as the tracer.

$$R_a = \left(\frac{R_{aD} - \left\{ p \times V \times \left[\frac{C(t_i) + C(t_{i-1})}{2} \right] \times \left[\frac{MPE(t_i) - MPE(t_{i-1})}{t_i - t_{i-1}} \right] \right\}}{\left\{ \frac{MPE(t_i) + MPE(t_{i-1})}{2} \right\}} \right) - R_{aD}$$

where R_a is the rate of appearance of glucose, R_{aD} is the infusion rate of $[6,6-^2\text{H}_2]$ glucose, $C(t_i)$ and $C(t_{i-1})$ represent the concentrations of unlabeled glucose at time t_i and t_{i-1} , and $MPE(t_i)$ and $MPE(t_{i-1})$ are the plasma enrichment of $[6,6-^2\text{H}_2]$ glucose at times t_i and t_{i-1} . The volume of distribution of glucose was assumed to equal 200 mL/kg, and the pool correction factor was assumed to be 0.65 (41).

In addition, $[6,6-^2\text{H}_2]$ glucose was used to trace the rate of appearance of $[^{14}\text{C}]$ glucose. To do so, the equations of Steele were again used, except that the ratio of the plasma concentration of $[6,6-^2\text{H}_2]$ glucose (*i.e.* the concentration of the tracer in millimoles per L) to the plasma concentration of $[^{14}\text{C}]$ glucose (*i.e.* the tracee concentration in disintegrations per min/L) was substituted for the molar percent enrichment, and the concentration of $[^{14}\text{C}]$ glucose (in disintegrations per min/L) was used for C. Rates of unlabeled and ^{14}C -labeled glucose appearance are expressed per kg lean body mass.

Flux through UDP-glucose pool was calculated as

$$\text{UDP glucose flux} = \left(\frac{F_{\text{Gal}}}{\text{SA of UDP} - [^{14}\text{C}] \text{glucose}} \right)$$

where F_{GAL} is the iv infusion rate of $[1-^{14}\text{C}]$ galactose, and the SA of UDP- $[^{14}\text{C}]$ glucose is the specific activity of acetaminophen $[^{14}\text{C}]$ glucuronide in urine (32, 42–44).

Statistical analysis

Data in the figures and text are expressed as the mean \pm SEM. Values observed from –30 to 0 min on each study day were meaned for each individual and considered the basal values. The area above or below basal was calculated using the trapezoidal rule. Paired Student's *t* test was used to test for within-group differences. A one-tailed test was used to test the hypotheses that the plasma glucose concentration and glycogenolysis were higher on nonsuppressed glucagon days than on suppressed glucagon study days. All other *t* tests were two-tailed. $P < 0.05$ was considered statistically significant.

Results

Plasma insulin and glucagon concentrations

Plasma insulin concentrations did not differ on the suppressed glucagon and nonsuppressed glucagon study days either before or after glucose ingestion (Fig. 1, upper panel). Insulin concentrations peaked at 130 ± 10 min after glucose ingestion. Glucagon concentrations (Fig. 1, lower panel) before glucose ingestion also did not differ on the suppressed glucagon and nonsuppressed study days (85 ± 7 vs. 80 ± 8 ng/L). Glucagon concentrations fell during the first 2 h of the suppressed glucagon study day to values that were lower ($P < 0.0001$) than those observed over the same interval on

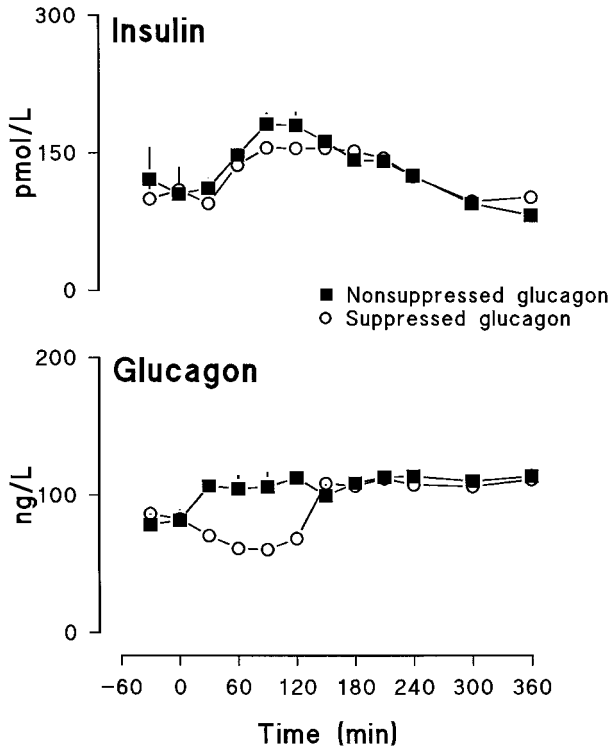


FIG. 1. Plasma insulin and glucagon concentrations observed on the glucagon-suppressed and nonsuppressed study days. A glucose drink was ingested at time zero.

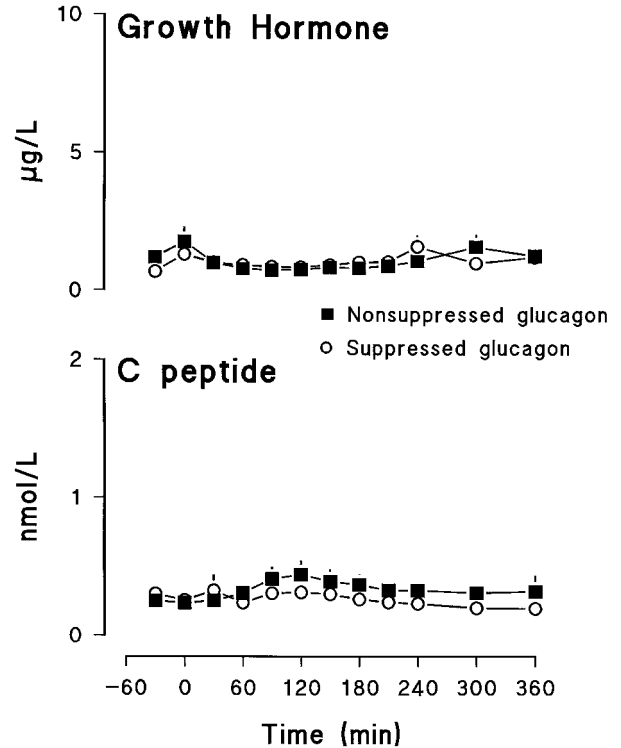


FIG. 2. Plasma GH and C peptide concentrations observed on the glucagon-suppressed and nonsuppressed study days. A glucose drink was ingested at time zero.

the nonsuppressed study day (66 ± 5 vs. 108 ± 7 ng/L). Glucagon concentrations on the suppressed study day increased at 120 min to values that no longer differed from those observed on the nonsuppressed study day.

Plasma C peptide and GH concentrations

GH concentrations remained constant and equal on the suppressed and nonsuppressed study days (Fig. 2, upper panel). Plasma C peptide concentrations before glucose ingestion did not differ on the 2 study days (Fig. 2, lower panel). Plasma C peptide concentrations increased after glucose ingestion on the nonsuppressed study day, but did not change on the suppressed study day. This resulted in plasma C peptide concentrations that were slightly, but significantly ($P < 0.01$), higher on the nonsuppressed than on the suppressed study day.

Plasma glucose concentrations

The plasma glucose concentration (4.6 ± 0.2 vs. 4.8 ± 0.1 mmol/L) did not differ before glucose ingestion on the suppressed and nonsuppressed study days (Fig. 3). After ingestion of glucose, the plasma glucose concentration increased, reaching a peak at 90 min of 9.2 ± 0.7 mmol/L on the suppressed study day in contrast to 10.9 ± 0.8 mmol/L on the nonsuppressed study day ($P < 0.001$). This resulted in the area above basal (1304 ± 268 vs. 1045 ± 258 mmol/L over 6 h) glucose concentration being lower ($P < 0.05$) on the suppressed than on the nonsuppressed study day. As anticipated, the difference in glucose concentration (569 ± 67 vs.

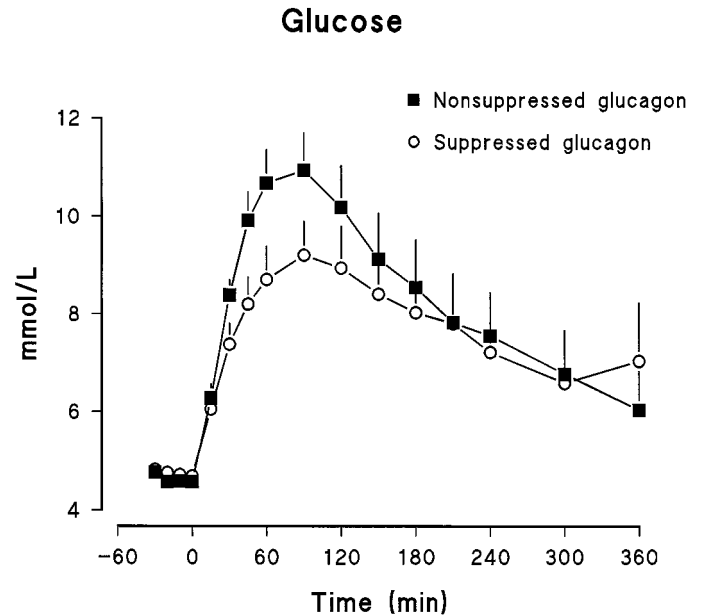


FIG. 3. Plasma glucose concentration observed on the glucagon-suppressed and nonsuppressed study days. A glucose drink was ingested at time zero.

396 ± 59 mmol/L over 2 h) was most marked ($P < 0.001$) during the first 2 h when glucagon concentrations differed.

Glucose appearance and disappearance

Rates of glucose appearance and disappearance did not differ before glucose ingestion on the 2 study days (Fig. 4).

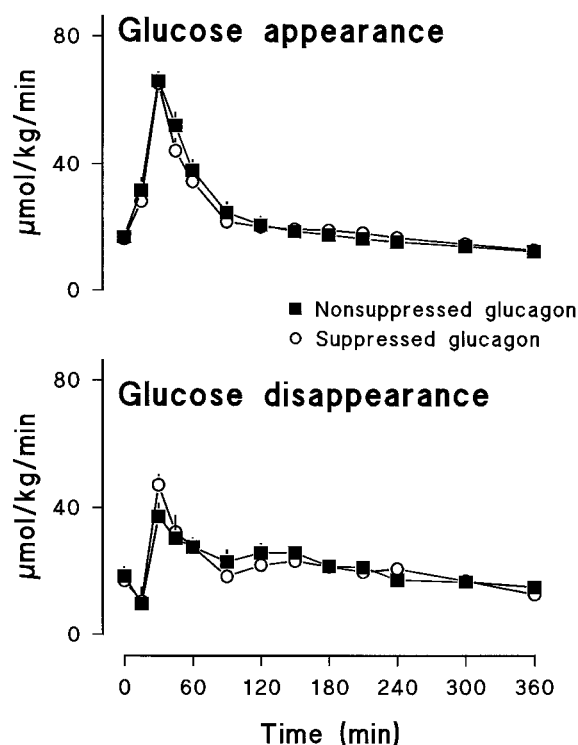


FIG. 4. Rates of glucose appearance and disappearance observed on the glucagon-suppressed and nonsuppressed study days. A glucose drink was ingested at time zero.

As glucose concentrations increased more after glucose ingestion on the suppressed than on the nonsuppressed study day, this by definition meant that glucose appearance exceeded disappearance. The increase in glucose appearance and disappearance above basal over the 6 h of study did not differ on the nonsuppressed and suppressed study days. However, glucose appearance during the first 2 h (*i.e.* when glucagon concentrations were different) was slightly ($P = 0.07$) higher on the nonsuppressed compared with the suppressed study days (4.3 ± 0.3 vs. 3.9 ± 0.3 mmol/kg \cdot 2 h).

Flux through UDP pool

The infusion rate of [14 C]galactose (6.38 ± 0.42 vs. $6.68 \pm 0.41 \times 10^3$ dpm/kg \cdot min), urinary UDP glucose specific activity (0.97 ± 0.10 vs. 1.09 ± 0.12 dpm/ μ mol; Fig. 5, upper panel), and UDP glucose flux (6.90 ± 0.52 vs. 6.50 ± 0.42 μ mol/kg \cdot min) did not differ on the nonsuppressed and suppressed study days (Fig. 5, lower panel).

[14 C]Glucose appearance

The rate of appearance of [14 C]glucose (in disintegrations per min/kg \cdot min) did not differ over the 6 h of study on the nonsuppressed and suppressed study days (Fig. 6). However, the rate of appearance of [14 C]glucose was greater ($P < 0.001$) during the first 2 h after glucose ingestion (*i.e.* when glucagon concentrations differed) on the nonsuppressed compared with the suppressed study day (1.74 ± 0.19 vs. $1.09 \pm 0.09 \times 10^5$ dpm/kg \cdot 2 h). The rate of appearance of [14 C]glucose increased at 120 min on the suppressed study

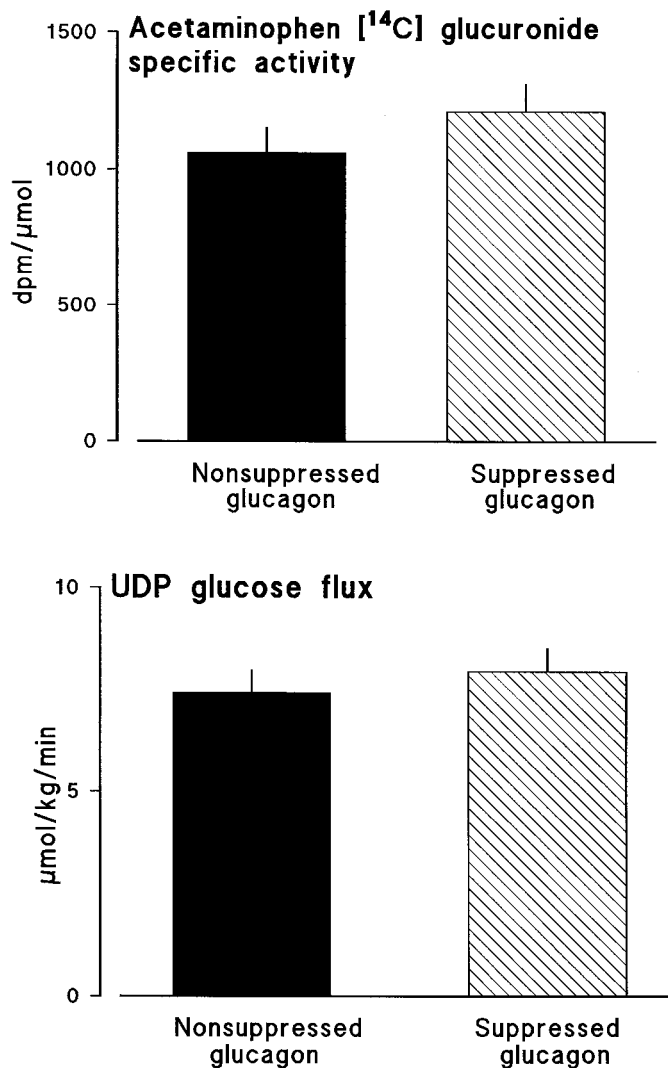


FIG. 5. Urinary acetaminophen [14 C]glucuronide specific activity and UDP glucose flux on the glucagon-suppressed and nonsuppressed study days. A glucose drink was ingested at time zero.

day coincident with the increase in glucagon concentration (see Fig. 1) to a rate that was slightly, but not significantly, higher than that observed on the nonsuppressed study day. As urinary [14 C]glucuronide (and presumably newly formed hepatic glycogen) specific activity did not differ on the 2 study days, the rate of appearance of unlabeled glucose derived from glycogen closely paralleled that of the systemic rate of appearance of [14 C]glucose.

Discussion

The present experiments demonstrate that lack of suppression of glucagon worsens glucose tolerance in subjects with type 2 diabetes mellitus. We previously demonstrated that it also does so in patients with type 1 diabetes mellitus (11). Taken together, these data indicate that inappropriately elevated glucagon concentrations can substantially increase postprandial glucose concentrations in both insulin-sensitive and insulin-resistant individuals.

We (10) and other investigators (26–29) have established

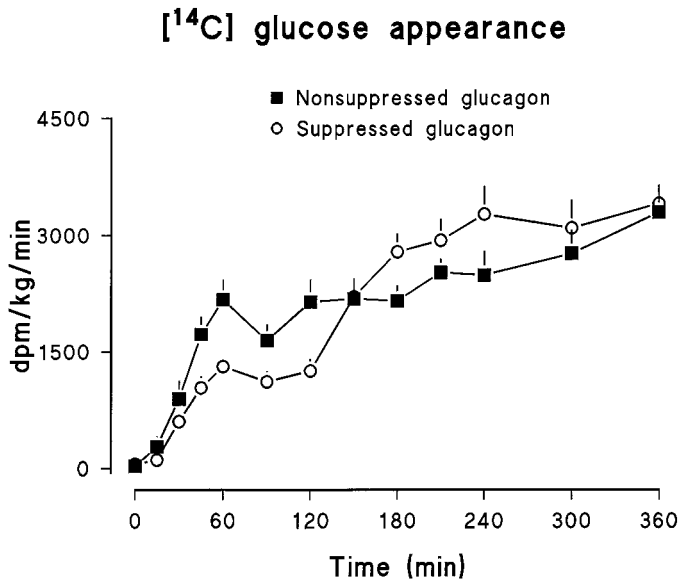


FIG. 6. [^{14}C]Glucose release from glycogen into the systemic circulation on the glucagon-suppressed and nonsuppressed study days. A glucose drink was ingested at time zero.

that the effect of glucagon on glucose metabolism is critically dependent upon the prevailing insulin concentration. Whereas lack of suppression of glucagon causes marked hyperglycemia in the presence of insulin deficiency, it has little if any effect on glucose tolerance in the presence of insulin sufficiency (10). In the current experiments a lack of glucagon suppression led to an approximately 1.5–2 mmol/L increment in postprandial glucose concentrations. Glucose concentrations were higher despite the fact that higher C peptide concentrations (and therefore portal insulin concentrations) also were higher on the nonsuppressed compared with the suppressed study days. This occurred because the low dose somatostatin infusion, although able to lower glucagon concentrations, was insufficient to completely offset the stimulatory effects of the higher glucose concentrations on insulin secretion on the nonsuppressed study day. Therefore, it is likely that the difference in glucose concentration would have been even greater if insulin concentrations had been better matched on the two occasions.

We have previously shown that lack of suppression of glucagon can increase postprandial glucose production (10, 11). However, those experiments did not determine the mechanism by which it did so. Although glucagon stimulates both glycogenolysis and gluconeogenesis, the time course of its effects on those two processes differs (45, 46). An acute increase in glucagon is accompanied by a rapid (within minutes) increase in glycogenolysis followed by a slower increase in gluconeogenesis (45, 46). The present experiments took advantage of the unique metabolism of galactose to determine whether a lack of suppression of glucagon leads to an increased rate of glycogenolysis. As previously discussed in detail (19, 35, 36, 47, 48), iv infused [$1\text{-}^{14}\text{C}$]galactose is quantitatively extracted by the liver. The [$1\text{-}^{14}\text{C}$]galactose is successively metabolized to UDP-[^{14}C]galactose, then to UDP-[^{14}C]glucose (32). UDP-[^{14}C]glucose can then either be incorporated into glycogen or directly converted to [^{14}C]glu-

cose-1-phosphate. Although the latter reaction is theoretically possible (35, 36, 48), flux in this direction will probably be trivial in the fed state because large amounts of glucose will be moving in the opposite direction toward glycogen. Therefore, it is likely that essentially all [^{14}C]glucose entering the systemic circulation in the present experiments first passed through glycogen.

The rate of appearance of [^{14}C]glucose progressively increased after glucose ingestion on both study days, indicating ongoing glycogenolysis. However, the rate of increase during the first 2 h after glucose ingestion was more rapid on the nonsuppressed than on the suppressed study day, implying a higher rate of glycogenolysis. This pattern changed at 2 h when the rate of appearance of [^{14}C]glucose increased on the suppressed day concurrent with the rise in plasma glucagon. These data strongly imply that the fall and subsequent rise in glucagon on the suppressed study day were accompanied by a slowing and a subsequent acceleration of the rate of glycogenolysis. This conclusion is based on the assumption that the outer layer of glycogen was equally labeled with [^{14}C]glucose on the 2 study days.

Comparable urinary [^{14}C]glucuronide specific activity on both study days supports, but does not prove, this assumption, as it merely reflects the integrated UDP glucose specific activity over the entire 6 h of the study. Time-dependent differences in hepatic UDP-glucose specific activity would not be detected. It is theoretically possible that the lower rate of release of [^{14}C]glucose during the first 2 h of the suppressed study day could have been due to lower rates of glycogen synthesis and, therefore, lower rates of incorporation of [^{14}C]glucose into glycogen. However, we believe this to be highly unlikely, because both *in vitro* (49, 50) and *in vivo* experiments (51, 52) have shown that lowering of glucagon if anything increases rather than decreases glycogen synthesis (52). Furthermore, flux through the UDP-glucose pool was the same on the 2 study days, supporting the assumption that total glycogen synthesis over the 6 h of the study was the same. This conclusion is consistent with the observation made by several investigators that an acute increase in glucagon causes a rapid increase in glycogenolysis (53). Our data appear to show the converse, in that a postprandial fall and a subsequent rise in glucagon are accompanied by a decrease and a subsequent increase in glycogenolysis. It remains to be determined in future studies whether parallel changes in gluconeogenesis occur.

The present studies suffer from several limitations. First, we do not know the actual portal glucagon concentrations that were present on the 2 study days. However, if hepatic extraction of glucagon was 40% (54, 55), then the peripheral venous glucagon concentration of approximately 90 ng/L present before the somatostatin infusion on the 2 study days was associated with a portal venous glucagon concentration of about 140 ng/L. Assuming that somatostatin resulted in comparable and near-complete inhibition of glucagon secretion, then the peripheral venous glucagon concentration of approximately 140 ng/L present after glucose ingestion on the nonsuppressed study day probably represented either no change or a slight increase in portal glucagon concentrations. This pattern mimics the no change or paradoxical rise in glucagon concentrations typically observed in people with

type 2 diabetes after food ingestion (1, 2, 6, 8). If hepatic glucagon extraction were somewhat higher (e.g. 50%), then we may have underreplaced the subjects on the nonsuppressed study day. The fact that the subjects ingested glucose rather than a mixed meal also could be considered a limitation. We used this approach because we were concerned that the low dose of somatostatin would not be adequate to inhibit glucagon secretion after the ingestion of a protein-containing mixed meal. If eating a mixed meal results in an excessive rise in glucagon in subjects with type 2 diabetes, then the impact of glucagon on glucose tolerance may be even greater than that observed in the present experiments.

We infused insulin in a diabetic insulin profile on both occasions. The insulin concentrations achieved in this study closely mimic those achieved in the postprandial phase in people with established type 2 diabetes mellitus (1, 13). We did so in an effort to be sure that each subject had adequate diabetic, albeit not normal, postprandial insulin concentrations, because we were concerned that the somatostatin infusion, by inhibiting already low endogenous insulin secretion, might create a state of severe insulin deficiency. Therefore, the effects of glucagon probably would have been larger if no insulin had been infused. We used somatostatin to inhibit endogenous hormone secretion along with infusions of insulin and GH to match hormone profiles on the 2 study days. Although it creates controlled experimental conditions, this approach obviously does not reflect real life conditions. Finally, we performed these studies after achieving euglycemia by means of an overnight infusion of insulin, thereby mimicking the metabolic situation likely to be present in well controlled type 2 diabetic subjects. The nocturnal insulin infusion may have improved hepatic insulin action (56), thereby dampening the response to glucagon. If so, we may have underestimated the impact that lack of suppression of glucagon would have in individuals with less well controlled diabetes.

In summary, the present experiments demonstrate that lack of suppression of glucagon can cause postprandial hyperglycemia in subjects with type 2 diabetes. The accelerated rate of release of [¹⁴C]glucose from glycogen suggests that this is due at least in part to an increase in the rate of glycogenolysis. Appropriately timed suppression of glucagon lowered postprandial glucose concentrations by about 1.5–2 mmol/L without causing subsequent hypoglycemia. These data suggest that agents that inhibit postprandial glucagon secretion or antagonize glucagon action will probably be useful in the treatment of patients with diabetes mellitus.

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