Hyperglycemia and β-Cell Adaptation During Prolonged Somatostatin Infusion with Glucagon Replacement in Man

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SUMMARY

To assess the relationship between β-cell function and the level and duration of hyperglycemia during generalized β-cell impairment, we studied the effects of acute and prolonged infusion of somatostatin in seven normal men. Twenty minutes after beginning an acute infusion of somatostatin (200 μg/h) plus glucagon replacement (0.75 ng/kg/min), plasma glucose (PG) remained unchanged, but plasma insulin (IRI) and acute insulin response to isoproterenol had fallen markedly. Seventy minutes after beginning somatostatin-plus-glucagon, a rise in PG was associated with an increase in the acute insulin response to isoproterenol, though not to the control level. In a separate study, after 46 h of the somatostatin-plus-glucagon infusion, at a glucose level similar to the 70-min level, plasma insulin had returned nearly to the control level and the acute insulin response to isoproterenol had returned completely to the control level. Such increases in basal and stimulated insulin secretion most likely represent a time-dependent adaptation by the β-cells to the persistent hyperglycemia. First- and second-phase insulin responses to intravenous glucose were markedly inhibited after 46 h of somatostatin-plus-glucagon. In summary, a 46-h infusion of somatostatin with glucagon replacement in humans leads to hyperglycemia, a slightly diminished basal insulin level, markedly decreased insulin responses to glucose, and an insulin response to isoproterenol maintained at a normal level by acute and probably chronic adaptation to the hyperglycemia. We speculate that β-cell adaptation to hyperglycemia may explain the similar abnormalities of islet function observed in patients with NIDDM. DIABETES 32:943–947, October 1983.

It has been observed in dogs that the infusion of des-Asn^5-[D-Trp^8-D-Ser^{13}]-somatostatin, a selective inhibitor of pancreatic β-cell function, leads to a large initial inhibition of acute insulin responses to arginine and isoproterenol. However, a rise in such insulin responses is observed during continued infusion of the somatostatin analogue for 3 h, concomitant with the development of hyperglycemia.[1] We have hypothesized that such potentiation of acute insulin responses to non-glucose stimuli by hyperglycemia contributes to the maintenance of β-cell function both acutely during infusion of the somatostatin analogue in dogs, and more chronically in some patients with non-insulin-dependent diabetes mellitus (NIDDM).[1,2] In the present study, we tested whether humans adapt to islet inhibitory effects of somatostatin and studied the relationship between the time course of such adaptation and changes of plasma glucose levels during prolonged somatostatin infusion.

MATERIALS AND METHODS

Seven normal paid male volunteers (age 18–29 yr) gave written informed consent before participation in a study approved by the University of Washington Human Subjects Committee. Their ideal body weight ranged from 93% to 114% of ideal (mean ± SEM = 104 ± 3%). None had medical illnesses, were taking medications, or had histories of diabetes mellitus in parents or siblings. Studies were performed at the University of Washington Clinical Research Center. Each subject received an infusion of somatostatin for 46 h on one occasion and an infusion of somatostatin for 1–2 h on a second occasion. Three subjects participated in a third study involving the infusion of glucose for 46 h. Subjects were admitted to the Clinical Research Center for 2 days before the 46-h studies and placed on standardized weight-maintaining diets. The daily diet consisted of four identical liquid meals, each containing 45% carbohydrate, 40% fat, and 15% protein. Blood samples were obtained through a 2-in., 18-gauge teflon catheter inserted into a superficial forearm vein. Drugs were administered through a 12-in., 18.5-gauge teflon catheter, which had been placed in an antecubital vein of the opposite arm.

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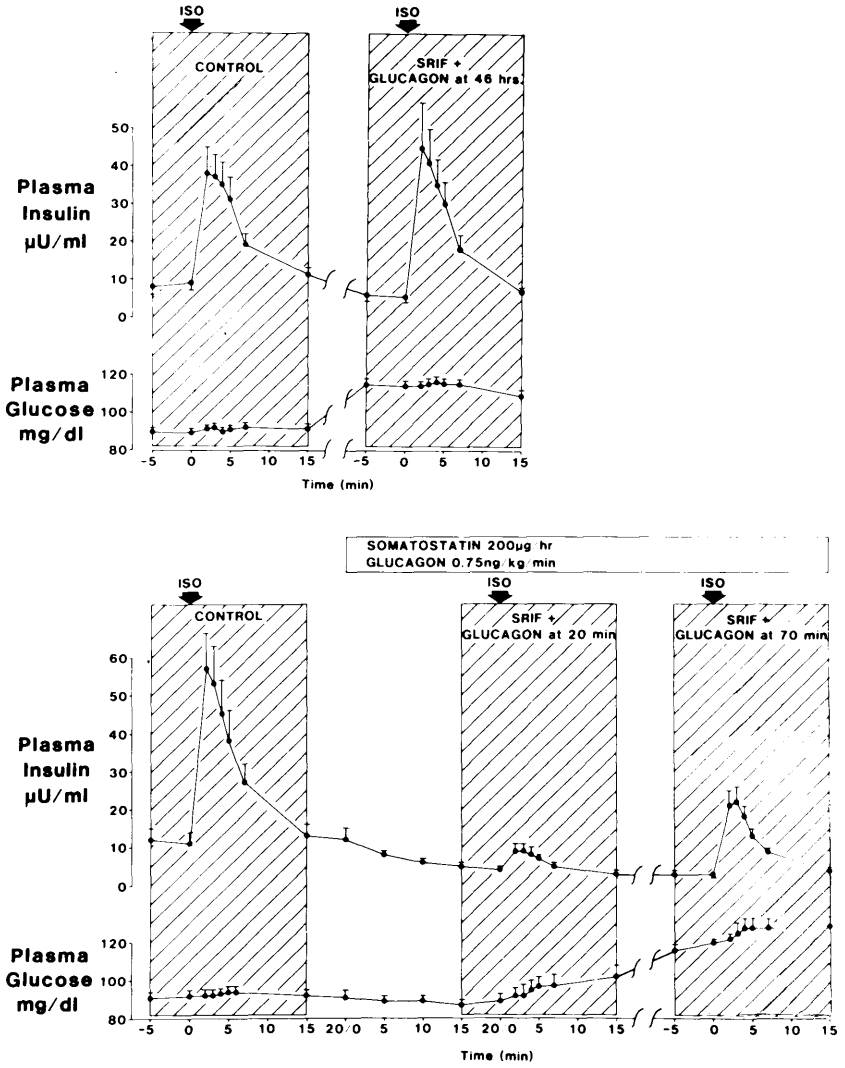

FIGURE 1. Effect of 46 h (upper panel) and 20–70 min (lower panel) of somatostatin (SRIF)-plus-glucagon infusion on plasma glucose and insulin levels and on the acute insulin response to 12 μg of isoproterenol (ISO) in seven normal subjects. Data expressed as mean ± SEM.

After 2 days of regulated diet and activity, the control insulin secretion study was initiated on the third day at 0900–1000 h, after a 15-h fast. At this time, isoproterenol (12 μg in 2 cc of saline) was administered as an intravenous bolus to determine the acute insulin response. Multiple blood samples for measurement of plasma insulin and glucose were obtained before and after the bolus. Additional baseline blood samples were drawn for measurement of plasma norepinephrine, epinephrine, and glucagon. Thirty minutes after the isoproterenol pulse, a primed (5 g) continuous (600 mg/min) glucose infusion was initiated. Insulin and glucose samples were obtained frequently after beginning the glucose infusion. At 1200 h on the same day (day 3), an infusion of cyclic somatostatin-14 (Beckman Instruments, Palo Alto, California) at 200 μg/h and glucagon at 0.75 ng/kg/min was initiated. This solution was delivered via a portable AC/battery volumetric infusion pump (IMED 960, IMED, San Diego, California). Meals were given at 0800, 1100, 1400, and 1700 h on days 1, 2, and 4, and at 1300, 1600, 1900, and 2200 h on day 3. At 0900–1000 h on day 5 (45–46 h after beginning the somatostatin-plus-glucagon infusion), the insulin secretion studies were repeated with samples obtained at the same times as on the control day (day 3).

After at least 1 wk on an ad libitum diet, subjects returned after a 15-h fast for the second study. Isoproterenol, 12 μg i.v., was administered to obtain a repeat control acute insulin response. Blood samples for plasma catecholamines, glucagon, glucose, and insulin levels were drawn at the same times as on the control day of the first study. Twenty minutes after the isoproterenol pulse, an infusion of somatostatin and glucagon was initiated at rates identical to those of the first study, and 20 min later, a 12-μg isoproterenol pulse was given and the acute insulin response measured. As the somatostatin-plus-glucagon infusion was continued, the subsequent rising glucose levels were measured every 5 min at the bedside with the use of a Beckman glucose analyzer (Beckman Instruments). An additional 12-μg isoproterenol pulse was administered and the acute insulin response measured when the plasma glucose had stabilized at the level previously attained after 46 h of the somatostatin-plus-glucagon infusion. The duration of the infusion of somatostatin-plus-glucagon necessary to raise the plasma glucose to the desired level was 70 ± 13 min (mean ± SEM, range 35–140 min).

Three subjects returned for a third study involving a prolonged glucose infusion to create hyperglycemia compa-

rable to that obtained during the somatostatin-plus-glucagon infusion. After obtaining fasting blood samples for plasma glucose and insulin levels, a 12-μg pulse of isoproterenol was given to obtain a control acute insulin response. An infusion of 10% dextrose in water was then initiated at a rate of 7.5 g of dextrose/kg/day. Forty-six hours after beginning the dextrose infusion, samples for fasting plasma glucose and insulin levels were obtained and a second 12-μg isoproterenol pulse was given to measure the acute insulin response.

Plasma insulin levels were assayed by a modification of the double-antibody method of Morgan and Lazarow.[3] Plasma glucose was measured by the autoanalyzer glucose-oxidase method (Technicon Instruments). Plasma glucagon was measured by radioimmunoassay, employing a C-terminally directed antiserum.[4] Plasma epinephrine and norepinephrine levels were measured by single-isotope enzymatic assay.[5] The acute insulin response to isoproterenol and glucose was calculated as previously described.[1,2] The second-phase insulin response was calculated as the area under the insulin curve from 15 to 40 min after beginning the glucose infusion, using the prestimulus insulin level as the baseline. Fasting plasma levels of glucose, insulin, glucagon, norepinephrine, and epinephrine are each expressed as the mean of the levels obtained 5 and 0 min before each isoproterenol pulse. The Wilcoxon signed rank test was used to test for differences between experimental conditions. Each subject served as his own control. Results are expressed as mean ± SEM.

RESULTS AND DISCUSSION

Basal and isoproterenol-stimulated plasma insulin levels obtained during the short-term infusion of somatostatin and glucagon are depicted in Figure 1 (lower panel). After 20 min of this infusion, the basal insulin level had fallen from a control value of 12 ± 3 to 5 ± 1 μU/ml ($P < 0.02$) and the acute insulin response to isoproterenol had fallen from 36 ± 8 to 4 ± 1 μU/ml ($P < 0.02$). By 70 ± 13 min after beginning the infusion of somatostatin-plus-glucagon, plasma glucose had risen to 118 ± 2 mg/dl ($P < 0.02$ as compared

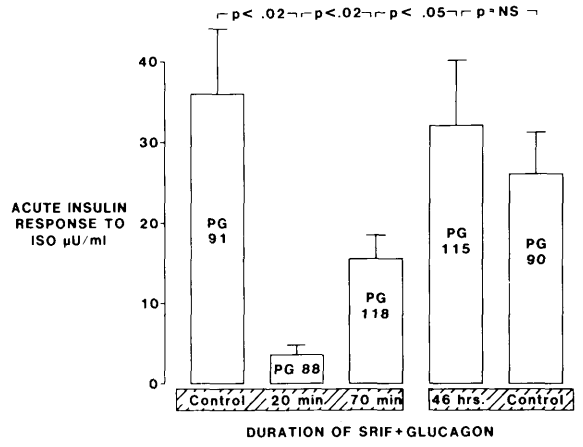

FIGURE 2. Comparison of the acute insulin response to isoproterenol (ISO) after 20 min, 70 min, and 46 h of the somatostatin (SRIF)-plus-glucagon infusion in seven normal subjects. PG = plasma glucose at which isoproterenol pulses were given. Data expressed as mean ± SEM.

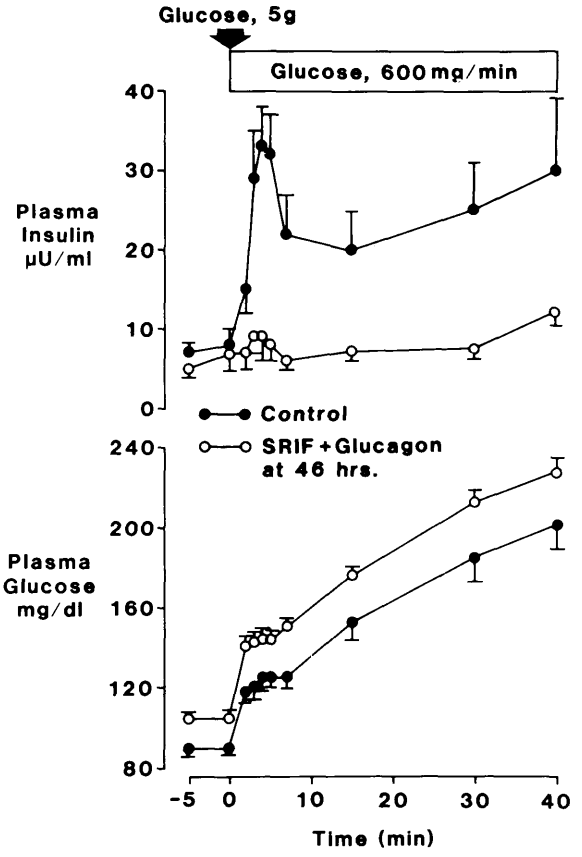

FIGURE 3. Effect of 46 h of somatostatin (SRIF)-plus-glucagon infusion on plasma glucose and on the insulin responses to a primed (5 g) continuous (600 mg/min) glucose infusion.

with the 20-min level), basal insulin had fallen further to 3 ± 1 μU/ml, the acute insulin response to isoproterenol had risen to 15 ± 3 μU/ml ($P < 0.02$, compared with the acute insulin response after 20 min of somatostatin), and the plasma glucagon level was unchanged from the control level [94 ± 6 versus 93 ± 6 pg/ml (control)].

Basal and isoproterenol-stimulated plasma insulin levels obtained before and after 46 h of the somatostatin-plus-glucagon infusion are also shown in Figure 1 (upper panel). The basal insulin level decreased slightly but consistently from a control value of 9 ± 2 to 6 ± 2 μU/ml after 46 h of the infusion ($P < 0.02$). Fasting plasma glucose increased during this period from 90 ± 2 to 115 ± 3 mg/dl ($P < 0.02$) and plasma glucagon remained unchanged [83 ± 7 (control) versus 89 ± 8 pg/ml]. As summarized in Figure 2, the acute insulin response to isoproterenol in the control state, 26 ± 5 μU/ml, was not significantly different from the insulin response obtained after 46 h of the infusion, 32 ± 8 μU/ml. The effect of long-term somatostatin on plasma glucose and insulin levels during the bolus-plus-infusion of glucose are shown in Figure 3. After 46 h of somatostatin-plus-glucagon, the first-phase insulin response to glucose had fallen from a control value of 23 ± 4 to 3 ± 1 μU/ml ($P < 0.02$), and the second-phase insulin response had fallen from 489 ± 120 to 80 ± 37 μU min/ml ($P < 0.02$).

After 46 h of the somatostatin infusion, as compared with the 70-min infusion, plasma glucose was not significantly different (115 ± 3 versus 118 ± 2 mg/dl), the basal plasma

insulin level was higher (6 ± 2 versus 3 ± 1 μU/ml, $P < 0.05$), and, as shown in Figure 2, the acute insulin response to isoproterenol was increased (32 ± 8 versus 15 ± 3 μU/ml, $P < 0.05$). There was no significant change of norepinephrine or epinephrine levels during either of these two studies.

In three subjects who received a 46-h glucose infusion, the fasting plasma glucose level increased from a baseline level of 88 ± 8 to 118 ± 17 mg/dl, values similar to the increase from 92 ± 4 to 118 ± 6 mg/dl observed in the same subjects during the somatostatin-plus-glucagon infusion. The 46-h glucose infusion resulted in a marked increase in the acute insulin response to isoproterenol in all three subjects from 15 ± 6 to 60 ± 17 μU/ml. This effect contrasts with the lack of change of the acute insulin response in the same subjects during prolonged infusion of somatostatin-plus-glucagon [22 ± 5 (control) versus 21 ± 7 μU/ml].

The increase in the acute insulin response to isoproterenol observed during the present study from 20 to 70 min was most likely caused by the concomitant increase in plasma glucose from 88 ± 4 to 118 ± 2 mg/dl. The present study thus extends previous findings in dogs[1] to humans, i.e., that the development of hyperglycemia during infusion of somatostatin leads to an adaptive response by potentiating the ability of the pancreatic β-cell to secrete insulin in response to non-glucose stimuli.

In addition to finding acute adaptation to hyperglycemia (potentiation of the insulin response to isoproterenol), we also observed that the basal insulin level and the insulin response to isoproterenol obtained after 46 h of somatostatin were consistently greater than after 70 min, despite similar glucose levels. A progressive decline in somatostatin's inhibitory effects due to time-dependent enhancement of endogenous somatostatin clearance or to downregulation of somatostatin action is one explanation for these findings, but seems unlikely since marked inhibition of both first- and second-phase insulin responses to glucose persisted (Figure 3).

Alternatively, the higher basal and stimulated insulin levels after 46 h of somatostatin may represent adaptation by the islets to the persistent hyperglycemia. Such adaptation may be caused by a time-dependent increase in the ability of glucose to stimulate basal insulin secretion and to potentiate the acute insulin response to non-glucose stimuli. In view of the chronicity of hyperglycemia in patients with NIDDM, such time-dependent β-cell adaptation may help to explain the findings of normal insulin levels and normal insulin responses to non-glucose stimuli in patients with NIDDM. Similar adaptation also appears to occur during glucose infusion in normal subjects, since insulin levels have been found to rise despite falling glucose levels from 2.5 to 20 h after beginning a 300-mg/min glucose infusion.[6] Such adaptive increases in insulin output may help to explain why it is difficult to create persistent, marked hyperglycemia in normal subjects by the infusion of glucose without simultaneously inhibiting β-cell function.[6,7]

The findings obtained when glucose alone was infused for 46 h indicate that infusion of somatostatin with glucagon replacement actually suppresses the β-cell response to isoproterenol in addition to suppressing the response to glucose. Although the acute insulin responses to isoproterenol after 46 h of somatostatin-plus-glucagon were equal to the preinfusion insulin responses, they were less than the response obtained at an equal degree of hyperglycemia in the absence of somatostatin. Nevertheless, the infusion of somatostatin-plus-glucagon caused greater suppression of the insulin responses to glucose than to isoproterenol.

We have considered other hormonal explanations for our findings. Since plasma levels of glucagon and catecholamines during the infusion were indistinguishable from preinfusion levels, it is unlikely that these hormones affected the insulin secretion findings. Prolonged infusion of somatostatin blocks endogenous bursts of growth hormone during meals and sleep, but does not appear to decrease basal growth hormone secretion.[8] Thus, although growth hormone has been reported to have effects on insulin secretion,[9] we feel it is unlikely that growth hormone perturbations could have accounted for our findings.

Thus, a 46-h infusion of somatostatin with glucagon replacement in humans leads to hyperglycemia, a slightly diminished basal insulin level, markedly decreased insulin responses to glucose, and an insulin response to isoproterenol maintained at a normal level by acute and probably chronic adaptation to the hyperglycemia. These findings are analogous to those in patients with NIDDM. Basal insulin levels in NIDDM, as compared with weight-matched controls, are similar[10] or slightly lower,[11] and C-peptide levels in NIDDM have been reported to be low.[11] Patients with NIDDM lack an acute insulin secretory response to glucose but maintain normal acute insulin responses to non-glucose secretagogues such as isoproterenol and arginine.[12] The similarities between measures of islet function in patients with NIDDM and normal subjects during prolonged somatostatin infusion lead us to speculate that β-cell adaptation to hyperglycemia may explain the similar abnormalities of islet function observed in patients with NIDDM.

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