Somatostatin reduces posthypoglycemic insulin resistance in insulin-dependent diabetes mellitus

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Abstract. In order to study whether somatostatin reduces posthypoglycemic insulin resistance, hypoglycemia was induced between 7.00 and 8.00 h by an iv infusion of insulin with and without somatostatin (250 μg/h) in 6 male patients with insulin-dependent diabetes mellitus (IDDM). Exogenous glucagon was infused to substitute for the suppression of its endogenous release (1.0–1.5 ng·kg⁻¹·min⁻¹). Insulin resistance was assessed by a somatostatin-insulin-infusion test (SIGIT) between 11.00 and 15.00 h. In the study without hypoglycemia, blood glucose was kept close to 6 mmol/l from 8.00 h until start of the SIGIT. In both hypoglycemic studies similar nadir blood glucose levels were achieved and hypoglycemia evoked the same increase of plasma epinephrine and cortisol, whereas plasma glucagon remained at its basal level. The growth hormone response to hypoglycemia was suppressed by somatostatin. At the onset of the SIGIT, the plasma levels of the counterregulatory hormones had returned to basal, and blood glucose and plasma free insulin concentrations were almost identical. During the SIGIT there were no differences in plasma free insulin or counterregulatory hormone levels. Insulin resistance, as seen following hypoglycemia, was not demonstrable in the study with somatostatin. It is concluded that somatostatin reduces insulin resistance following hypoglycemia in patients with IDDM. It is therefore suggested that an analogue with a specific GH release inhibiting property may be useful in reducing glycemic instability when given as adjunct therapy to insulin in patients with labile glycemic control.

Intensified insulin therapy in patients with insulin-dependent diabetes mellitus (IDDM), aiming at near normoglycemia, is associated with an enhanced risk for the occurrence of hypoglycemic episodes (Pramming et al. 1985). It is still a matter of controversy whether such hypoglycemic episodes may cause labile glycemic control by promoting posthypoglycemic insulin resistance (Raskin 1984). We have previously demonstrated insulin resistance to occur some 4–6 h after a hypoglycemic event (Kollind et al. 1987a, 1988a), and that growth hormone is of importance in this respect (Kollind et al. 1988b). Against this background the use of the GH release inhibiting hormone somatostatin may seem a fruitful therapeutic option in an attempt to circumvent this metabolic consequence of hypoglycemia. Therefore, the aim of the present study was to assess the effect of somatostatin, administered during hypoglycemia, on posthypoglycemic insulin resistance in IDDM patients. In order to simulate the action of a specific inhibitor of GH secretion, exogenous glucagon was given to compensate for the somatostatin-induced suppression of glucagon secretion.

Patients and Methods
Six male patients with IDDM, age 22–37 years, without residual beta-cell function (C-peptide < 0.1 nmol/l after a mixed meal) were studied. The duration of their diabetes was 9.4 ± 1.9 years, the body mass index (Thomas et al. 1976) 23.5 ± 0.8 and HbA₁c 8.1 ± 0.4% (normal < 5.6%). Their regular daily insulin dose was 45.7 ± 1.9 IU, divided in two, three or four injections.
Their plasma level of antibody-bound insulin was 5.3 ± 3.6%. None had hypertension, albuminuria or signs of peripheral neuropathy. Their autonomic nervous function as assessed by theValsalva ratio and respiratory sinus arrhythmia was normal. None was taking other medication than insulin. The subjects were recruited from our out-patient clinic and were not selected on the basis of previous manifestations of metabolic brittleness. Informed consent was obtained from all subjects and the local Ethics Committee had approved the study.

In order to deplete the sc insulin depot, the patients had their last sc insulin injection 30—40 h prior to the study. Twenty-four hours before the study, they were admitted to a metabolic ward and given regular insulin (Actrapid®, Novo Industri ½%, Denmark) as a variable iv infusion, adjusted every 1—3 h according to the capillary blood glucose concentration, aiming at a level between 8—10 mmol/l over the day, and as close as possible to 6 mmol/l at 7.00 h on the following morning. The patients had their regular meals and snacks during this period (day 1) but no food was ingested after 22.00 h. The insulin infusion allowed the patients to walk inside the hospital but not to perform heavy exercise.

On the following morning at 7.00 h (day 2), the experiments were started. The patients were placed in comfortable semirecumbent position and a short teflon catheter was inserted into a forearm vein on each side, one being used for blood sampling and the other for hormone infusions. Each patient participated in three experiments, at least 1 week elapsing between two tests. Between 11.00 and 15.00 h in all the studies, insulin resistance was assessed by a modified somatostatin (100 µg/h)-insulin (0.4 mIU·kg⁻¹·min⁻¹)-glucose (4.5 mg·kg⁻¹·min⁻¹)-infusion test (SIGIT) (Harano et al. 1977). Prior to SIGIT, i.e. between 7.00 and 11.00 h, the following protocols were used:

- Study A: no hypoglycemia.
- Study B: hypoglycemia induced by insulin.
- Study C: hypoglycemia induced by insulin, with co-infusion of somatostatin and glucagon.

In study A the blood glucose level was kept at 5—6 mmol/l by a variable iv insulin infusion, whereas in study B, a constant rate iv insulin infusion (1.5 mIU·kg⁻¹·min⁻¹) was started at 7.00 h and maintained until a blood glucose level below 2.5 mmol/l was reached. After 20 min the hypoglycemic reaction was stopped by an iv bolus injection of glucose (0.15 g/kg). Sixty min after the hypoglycemia, the variable iv insulin infusion was restarted, its rate being adjusted every 5—15 min, in order to keep the blood glucose level close to 6 mmol/l at the start of the SIGIT. In study C, insulin was given as in study B, and the same glucose dose was applied to stop the hypoglycemic reaction. In addition, from 7.00 to 11.00 h somatostatin (250 µg/h, Ferring AB, Sweden) and glucagon (Novo Industri ½%, Denmark) were infused through separate iv lines. Glucagon was infused at a rate of 1.0 ng·kg⁻¹·min⁻¹, except during maximal hypoglycemia, when its rate was temporarily increased to 1.5 ng·kg⁻¹·min⁻¹ for 20 min. In order to simulate the same blood glucose profile as in study B, additional iv glucose was given in the pre-SIGIT period. Therefore, with the chosen experimental design, studies A and B were performed in random order, whereas study C was done as the last test.

Venous blood samples were obtained every 15—60 min between 7.00 and 15.00 h on day 2, for measurements of blood glucose (Glucose analyzer 23 AM, Yellow Springs Instruments Inc, USA), plasma free insulin (Nakagawa et al. 1973), GH (Cerasi et al. 1966), cortisol (Lantto et al. 1983) and glucagon (Faloona & Unger 1974). Plasma epinephrine (Hallman et al. 1978) was analysed every 30 min between 7.00 and 11.00 h. The levels of glycosylated hemoglobin concentration (Jeppson et al. 1978), plasma antibody-bound insulin (Nakagawa et al. 1973) and C-peptide (Heding 1975) were determined by previously described methods. The blood glucose M-value was calculated according to Schlichtkrull et al. (1965).

For the statistical analysis Friedman's non-parametric analysis of variance and Wilcoxon's signed rank test were used. Data are given as means ± SEM.

Results

The mean blood glucose during the 24-h period preceding each experiment was close to identical in studies A, B and C (8.9 ± 0.6, 9.0 ± 0.5 and 8.8 ± 0.3 mmol/l), and the corresponding M-values were similar (18.1 ± 2.2, 17.0 ± 4.0 and 20.7 ± 2.2).

Between 7.00 and 11.00 h on day 2, plasma epinephrine, cortisol, GH and glucagon were in the normal range in study A (Fig. 1). Insulin-induced hypoglycemia (study B) caused the expected rises of plasma epinephrine, cortisol and GH, whereas no significant glucagon rise was registered. In study C, the magnitude of hypoglycemia and the corresponding increases of plasma epinephrine and cortisol were similar to those seen in study B, and plasma glucagon remained at its basal level. The plasma GH levels, calculated as the area under the respective curve between 7.00 and 11.00 h (pre-SIGIT period), were 9.7 ± 2.2, 78.6 ± 7.2 and 3.4 ± 1.8 µg/l per h in the study A, B and C, respectively. Thus, somatostatin suppressed the GH response to hypoglycemia (P < 0.01) and the basal secretion of GH (P < 0.05).
Blood glucose, plasma free insulin, glucagon, epinephrine, cortisol and growth hormone levels (mean ± SEM) between 7.00 and 15.00 h in the 6 patients, studied in relation to three metabolic interventions, i.e. with no hypoglycemia (Study A: ± SEM as shaded area), with hypoglycemia induced by insulin (Study B: – – –), and with hypoglycemia induced by insulin concomitant with somatostatin and glucagon (Study C: ▲ – ▲). Insulin resistance between 11.00 and 15.00 h was evaluated by SIGIT (see Patients and Methods).

**Table 1.**
Blood glucose levels during the SIGIT.

<table>
<thead>
<tr>
<th></th>
<th>11.00 h</th>
<th>12.00 h</th>
<th>13.00 h</th>
<th>14.00 h</th>
<th>15.00 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study B</td>
<td>5.8 ± 0.3</td>
<td>9.6 ± 0.3**</td>
<td>12.0 ± 0.5**</td>
<td>12.9 ± 0.7**, **</td>
<td>12.6 ± 0.6**, **</td>
</tr>
<tr>
<td>Study A</td>
<td>6.0 ± 0.2</td>
<td>9.2 ± 0.5</td>
<td>10.9 ± 0.8</td>
<td>11.7 ± 0.7</td>
<td>10.8 ± 0.9</td>
</tr>
<tr>
<td>Study C</td>
<td>5.8 ± 0.2</td>
<td>8.4 ± 0.5***</td>
<td>9.4 ± 0.9***</td>
<td>9.7 ± 1.1***</td>
<td>9.4 ± 1.2</td>
</tr>
</tbody>
</table>

Study B vs Study A, *P < 0.05. Study B vs Study C, **P < 0.05. Study C vs Study A, ***P < 0.05.
The total amount of insulin given between 7.00 and 11.00 h in study A, B and C was 2.1 ± 0.3, 7.5 ± 0.6 and 6.8 ± 0.6 IU, respectively. Although similar amounts of insulin were given in studies B and C, significantly more glucose was given prior to the SIGIT in study C as compared with study B (152 ± 16 vs 38 ± 2 g, P < 0.001). At the start of the SIGIT the plasma levels of epinephrine, glucagon, cortisol and GH were at basal levels, and almost identical concentrations of blood glucose and plasma free insulin were registered. During the SIGIT, plasma free insulin, GH, cortisol and glucagon did not differ in the three experiments (Fig. 1).

In study B as compared with study A, a higher blood glucose level (P < 0.05) was seen over the last hour of the SIGIT period (Fig. 1 and Table 1), whereas in study C the blood glucose level was lower than in study B (P < 0.05) during the last 3 h of the SIGIT period. In study C, as compared with study A, the blood glucose concentration was diminished over the whole SIGIT period, reaching statistical significance at 12.00, 13.00 and 14.00 h (P < 0.05) (Table 1).

Discussion

Total insulin resistance can be estimated in vivo over several hours with the modified SIGIT, a method with good accuracy and reproducibility (Kollind et al. 1987a, 1988b). By using this method in the present study we could demonstrate that posthypoglycemic insulin resistance can be reduced by the administration of somatostatin. Such an effect of this peptide has previously not been reported. However, adjunct therapy with somatostatin has been proposed in the treatment of patients with poorly controlled IDDM (Gerich et al. 1974; Meissner et al. 1975; Christensen et al. 1978), as it inhibits the secretion of glucagon and GH, both of which are secreted in excess in such patients (Unger et al. 1970; Hayford et al. 1980). Moreover, as GH has been implicated to be of particular importance for the pathogenesis of the dawn phenomenon, i.e. the hypoglycemic trait seen in IDDM patients in the morning hours (Campbell et al. 1985a), somatostatin has been successfully used to prevent this phenomenon to occur (Campbell et al. 1985b). Furthermore, since somatostatin also may modulate the intestinal absorption of nutrients (Wahren & Felig 1976), a beneficial effect of somatostatin in reducing postprandial hypoglycemia has been speculated upon (Bratusch-Marrain et al. 1981). For that reason our experiments were performed in the fasting state, thereby excluding the possibility that such effects would influence the results.

Somatostatin exerts no intrinsic effects on hepatic and peripheral glucose metabolism (Baron et al. 1987), but inhibits the secretion of several hormones including insulin. As only C-peptide negative patients participated in our study, such an inhibitory effect on the beta-cells would be of no importance here.

In the present study the restitution of blood glucose after hypoglycemia was impaired by somatostatin, as this peptide increased the need of additional glucose. The capacity of somatostatin to enhance insulin-induced hypoglycemia has been attributed to its suppression of glucagon secretion (Rizza et al. 1979). Although the glucagon response to hypoglycemia is impaired in most patients with IDDM, a further reduction in the secretion of glucagon, induced by somatostatin, could add to the defect glucose counterregulation in conjunction with insulin-induced hypoglycemia. For that reason we tried to compensate for this suppression of the endogenous glucagon secretion by exogenous glucagon. Indeed, similar peripheral venous plasma levels of glucagon were thus achieved in the two hypoglycemic studies. However, as the main action of glucagon is in the liver, the circulating levels in the portal vein are critical. With respect to a portal to peripheral vein glucagon ratio of about 1.7 (Blackard et al. 1974) we must consider that the infusion of glucagon did not fully compensate for a reduction in portal plasma glucagon levels. Thus, the increased need of iv glucose seen before start of the SIGIT may, at least partly, be explained by deficient glucagon action on the hepatic glucose production over this time period. Ipp et al. (1987) recently reported that somatostatin, in doses similar to those used here, impaired the metabolic clearance rate of exogenous insulin as they observed higher plasma insulin levels and an exaggerated hypoglycemic effect when insulin was given together with somatostatin. Consequently impairment of the clearance of exogenous insulin by somatostatin may be a further factor to consider in this respect. In our study the plasma free insulin level did not increase when somatostatin was infused. It therefore seems
unlikely that the influence of somatostatin on insulin clearance mediated the blood glucose lowering effect of the peptide seen here. It is, however, important to emphasize that the above discussed possible differences in portal vein glucagon concentrations and metabolic clearance rates of insulin concern the pre-SIGIT period only, whereas during SIGIT identical protocols were used in the three sets of experiments. During the SIGIT, plasma free insulin and counterregulatory hormone levels were close to identical. Thus the difference in insulin resistance seen between the experiments with and without hypoglycemia would be attributed to metabolic events prior to the SIGIT. With respect to insulin itself, the insulin infusion rate was temporarily increased, yielding transient hyperinsulinemia over about 90 min in our studies with hypoglycemia. Such a hyperinsulinemia cannot explain this effect, however, since Bolli et al. (1984) were unable to demonstrate insulin resistance following hyperinsulinemia when hypoglycemia was prevented by an iv glucose infusion. Other possibilities would include long-lasting diabetogenic effects of the counterregulatory hormones released in connection with the hypoglycemic episode. We have previously demonstrated that a transient increase in GH, with and without a concomitant release of other counterregulatory hormones, induces insulin resistance after a delay of about 4 h (Kollind et al. 1987b, 1988a). The finding of reduced posthypoglycemic insulin resistance by somatostatin adds further evidence for a key role played by GH in this context.

We observed lower blood glucose levels during the SIGIT in the experiment with hypoglycemia and somatostatin, indicating enhanced insulin sensitivity, in comparison with the experiment without hypoglycemia. As discussed above, differences in hormone concentrations in the pre-SIGIT period could be of importance for insulin sensitivity during the SIGIT because of the suppressive effect of somatostatin on the secretion of glucagon and GH. The possibility of a sustained and enhanced insulin sensitivity following a period of depressed glucagon secretion has previously not been studied in detail and available data do not support such an effect (Clausen et al. 1987). On the other hand, suppression of the GH-secretion could explain such an effect, as indicated above, since in the experiment with somatostatin, the plasma GH concentration was significantly diminished also in the pre-SIGIT period. Our data therefore support previous observations that suppression of the basal GH secretion enhances insulin sensitivity (Campbell et al. 1985b).

In conclusion, we suggest that an analogue of somatostatin which exclusively suppresses GH secretion could be of interest as an additional therapeutic agent in the treatment of diabetes as such a peptide might reduce the hypoglycemic rebound after hypoglycemia in diabetic patients with metabolic brittleness.

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References


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