Induction of β-Cell Rest in Type 1 Diabetes

Studies on the effects of octreotide and diazoxide

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OBJECTIVE — To evaluate the inhibitory effects of octreotide and diazoxide on insulin secretion in patients with type 1 diabetes and measurable levels of circulating C-peptide.

RESEARCH DESIGN AND METHODS — Diazoxide was given to six patients during a 7-day period (100 mg three times daily), followed by a 3-week washout. Subsequently, octreotide (50 μg, three times daily) was administered subcutaneously for 7 days. Pre- and postprandial blood glucose and serum C-peptide concentrations were measured before medication (control) and on day 7 of each medication period. Glucagon-stimulated C-peptide was determined in the morning before medication and on the day after each treatment period.

RESULTS — Diazoxide inhibited glucagon-stimulated C-peptide secretion (mean increment 0.08 nmol/l vs. 0.18 nmol/l, $P < 0.05$), whereas octreotide had no such effect. Both reduced the pre- and postprandial serum C-peptide concentrations ($P < 0.05$), octreotide being the more potent in this respect. A reduction in basal and meal-related blood glucose was observed during octreotide treatment, whereas the glucose concentrations tended to be higher during treatment with diazoxide than during the 24-h control period.

CONCLUSIONS — The study indicates that the two drugs reduce insulin output by different mechanisms. Diazoxide inhibits hormonal release directly on the β-cells, whereas octreotide exerts its effect indirectly, presumably by multiple actions on insulin sensitivity and insulin-releasing hormones. The results suggest that each drug is capable of inducing β-cell rest in type 1 diabetes.

Hyperglycemia due to inadequate insulin secretion is a hallmark in the development of diabetes. The high glucose levels are thought to impair the secretory function of the insulin-producing β-cells (glucose toxicity) both in type 2 diabetes and in the early stages of type 1 diabetes (1,2). We have suggested that in autoimmune diabetes, hyperglycemia might increase the expression of islet cell autoantigens, thereby facilitating an autoimmune destruction of the islets. This suggestion is supported by results from experimental studies in which it has been shown that glucose (3–5) and insulin secretion (6) increase the production of islet cell autoantigens. In a recent clinical trial, we found that diazoxide, a K^+-channel opener that inhibits insulin secretion and reduces autoantigen expression in vitro (6) and in vivo (7), improved the residual β-cell function in patients with new-onset autoimmune diabetes (8). This indicates that β-cell rest might be beneficial to the course of type 1 diabetes (9). In a search for alternative drugs to reduce β-cell activity, we choose to examine the effect of octreotide.

Octreotide, a somatostatin analog, is widely used in clinical practice for its capacity to inhibit secretion from endocrine cells (10) and is most commonly used in the treatment of acromegaly. In such patients, glucose tolerance is improved (11) and insulin secretion decreased, effects partly attributable to the growth hormone–lowering effects of the drug (12). It is known that somatostatin and its analogs also inhibit glucagon release (13). Furthermore, octreotide was recently found to increase insulin-stimulated glucose uptake directly in the perfused human forearm through local, yet undefined, mechanisms (14).

The purpose of the present study was to compare the effects of octreotide and diazoxide with respect to their ability to inhibit insulin secretion in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— The study comprised six patients (three men and three women, mean age 27.25 years, range 22–31) with type 1 diabetes, diagnosed on clinical criteria. They had been treated with multiple insulin injections (regular insulin at mealtimes and NPH insulin at bedtime) for a mean of 4 years (range 1–10 years) and displayed some residual β-cell function, as evidenced by detectable levels of C-peptide.

At the start of the study, basal and glucagon-stimulated C-peptide concentrations were determined, and during 1 day, blood samples were taken before breakfast, lunch, and dinner and 45 min after each meal for blood glucose and serum C-peptide assays. Subsequently, the patients were admitted to the clinic and diazoxide (100 mg three times daily) was given orally for 1 week. On day 7, blood samples were taken before breakfast, lunch, and dinner and 45 min after each of these meals for glucose and C-peptide assays. Then, after an overnight fast, blood was collected for measurements of basal and glucagon-stimulated C-peptide concentrations. After a 3-week washout period, the patients were given octreotide as subcutaneous injections, 50 μg three times daily before meals for 1 week. Blood sampling was carried out as described above. The following morning (day 8), 10–12 h after the last dose of octreotide, basal and glucagon-stimulated C-peptide concentrations were measured at 0 and 6 min after an intravenous injection of 0.5 mg glucagon. C-peptide (reference range in the fasting state 0.25–1.0 nmol/l)

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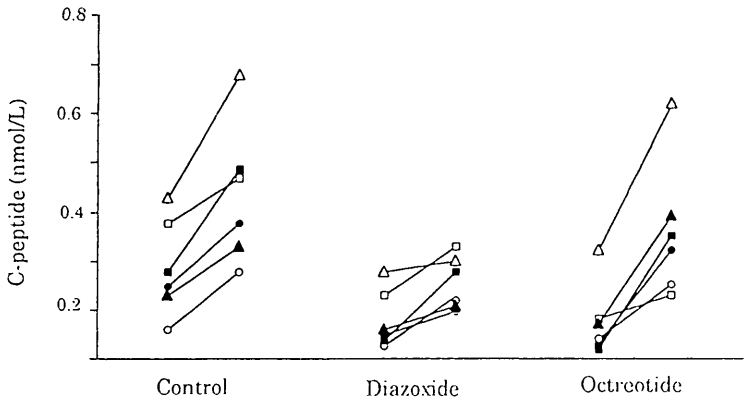

Figure 1—*Basal and glucagon-stimulated C-peptide concentrations in six patients with type 1 diabetes and residual insulin secretion, determined at the start of the study (control), after 1 week of diazoxide medication (100 mg three times daily), and after 1 week of medication with octreotide (150 μg daily). See METHODS for details. The multiple symbols represent individual patients.*

was determined with a radioimmunoassay in use at the Department of Clinical Chemistry, University Hospital, Uppsala, Sweden. HbA_{1c} (reference range 3.8–5.2%) was measured before the study and on day 7 during each treatment period. Throughout the study, the patients were instructed to adjust their insulin doses in accordance with the self-monitored blood glucose.

Statistics

The data, given as means ± SE, were analyzed by the paired *t* test and by factorial and repeated measures analysis of variance.

RESULTS

Glucagon-stimulated insulin secretion

At the start of the study, all patients had detectable C-peptide levels, which increased after injection of glucagon (from 0.28 ± 0.04 to 0.43 ± 0.06 nmol/l; $P < 0.0024$). After 7 days of diazoxide medication, the basal C-peptide concentrations was lower and the response to glucagon was reduced (from 0.17 ± 0.02 to 0.25 ± 0.02 nmol/l; $P < 0.0081$) compared with the response before treatment ($P < 0.05$). The basal C-peptide concentration was also lowered after 1 week of treatment with octreotide. However, the glucagon-stimulated response at the end of that period was similar to that seen at the start of the study (increase in C-peptide from 0.18 ± 0.03 to 0.36 ± 0.06 nmol/l; $P < 0.0038$) (Fig. 1).

Meal-stimulated insulin secretion and blood glucose concentrations

The effects of medication with diazoxide and octreotide on pre- and postprandial C-peptide levels are illustrated in Fig. 2. Both drugs lowered the insulin secretion compared with the control value ($P < 0.05$), and octreotide was more potent than diazoxide throughout the day. Blood glucose tended to be higher during the diazoxide treatment than before treatment, whereas during octreotide medication, lower blood glucose values were found. In particular, the postprandial glucose levels during the octreotide period were lower than those during the control and diazoxide periods (Fig. 3).

Before entering the study, the patients displayed a mean HbA_{1c} of 5.4 ± 0.7%, and their mean dose of exogenous insulin taken was 0.39 ± 0.04 IU · kg^{-1} · day^{-1}. These values did not change significantly after 1 week of treatment with diazoxide (5.3 ± 0.6% and 0.40 ± 0.03 IU · kg^{-1} · day^{-1}, respectively) or octreotide (5.0 ± 0.4% and 0.43 ± 0.03 IU · kg^{-1} · day^{-1}, respectively). Mean BMI was 24.8 ± 0.8 kg/m^2 before the study and raised during medication with diazoxide, probably due to fluid retention (25.6 ± 0.75 kg/m^2, $P < 0.05$), whereas no significant difference was observed after octreotide treatment (24.6 ± 0.8 kg/m^2).

CONCLUSIONS — In this study, diazoxide markedly inhibited glucagon-stimulated insulin release, whereas octreotide had virtually no effect. By contrast, the meal-stimulated C-peptide levels were more reduced by octreotide than by diazoxide. Octreotide also lowered the 24-h glucose concentration compared with the control value, whereas diazoxide did not.

Diazoxide is known to act on the insulin-producing β-cells by opening ATP-sensitive K^+-channels (15) and thereby directly inhibiting insulin release. This effect is used in the treatment of patients with hypoglycemia and abnormal insulin production, e.g., in insulinoma (16) and nesidioblastosis (17). In addition to its effects on the β-cells, diazoxide also has extrapancreatic effects (e.g., on vascular K^+-channels), as illustrated by its ability to lower the blood pressure upon intravenous administration (18). Further, edema and increased hair growth are common side effects of continuous oral treatment with diazoxide. This might reflect actions of the drug on ATP-sensitive K^+-channels in other tissues (19), although this has not been clarified.

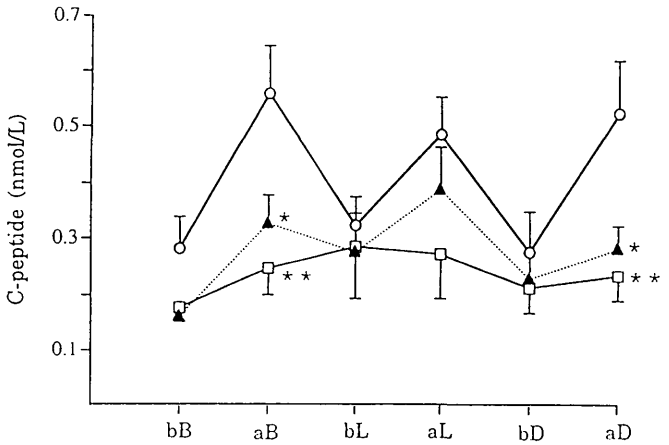

Figure 2—*Pre- and postprandial C-peptide concentrations in six patients with type 1 diabetes, determined at the start of the study (basal), after 1 week of diazoxide medication (100 mg three times daily), and after 1 week of octreotide medication (150 μg daily). ○, control group; ▲, diazoxide group; □, octreotide group. See METHODS for details. *P < 0.05 compared with the basal value. **P < 0.01 compared with the basal value. bB, aB = before and after breakfast; bL, aL = before and after lunch; bD, aD = before and after dinner.*

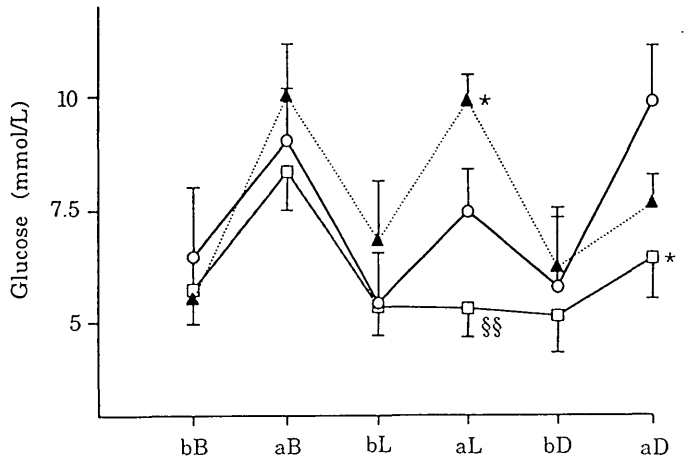

Figure 3—*Pre- and postprandial blood glucose concentrations in six patients with type 1 diabetes, determined at the start of the study (basal), after 1 week of diazoxide medication (100 mg three times daily), and after 1 week of octreotide medication (150 μg daily). ○, control group; ▲, diazoxide group; □, octreotide group. See METHODS for details. *P < 0.05 compared with the basal value. **P < 0.01 compared with the basal value. §§P < 0.01 octreotide compared with diazoxide period. bB, aB = before and after breakfast; bL, aL = before and after lunch; bD, aD = before and after dinner.*

Diazoxide treatment has met with variable success in patients with nesidioblastosis, whereas octreotide may lower insulin output in these cases as well (20). The basic defect in nesidioblastosis has recently been identified as mutations in either of the two subunits of the ATP-sensitive K^+-channel (21–23), which discovery has shed new light on the cause of the differential response to diazoxide and octreotide.

In the present study, octreotide had virtually no effect on glucagon-stimulated insulin release. On the other hand, the octreotide regimen was associated with a significant reduction of diurnal glucose and insulin levels, suggesting that the effects of octreotide are exerted at another level than through a direct inhibitory action on insulin release from the β-cells. This notion is supported by studies in the perfused rat pancreas, where octreotide had little or no effect in reducing insulin secretion (24). In healthy individuals, octreotide has been found to inhibit postalimentary hyperglycemia and to lower insulin levels (25). Also, in patients with diabetes, both type 1 and type 2, octreotide lowers the hyperglycemia after meals (26,27) and frequently reduces the insulin requirement (28). Taken together, our own results and data from others suggest that octreotide may reduce glucose and insulin concentration by its inhibitory action on glucose counterregulatory hormones (29). Alternatively, inhibition of gut hormones with incretin effects or a decrease in gastric motility may also determine the glycemic and insulin excursions after meals (24,30).

In addition, octreotide has been reported to increase insulin sensitivity (31–35) and to enhance glucose uptake in skeletal muscle (13). In a study of Zucker rats, improved insulin sensitivity has been observed after treatment with diazoxide (36). In the present study, however, a decrease in C-peptide levels during diazoxide treatment was accompanied by increased glucose concentrations, suggesting that in these patients the drug had no effect on insulin sensitivity.

In summary, the results indicate that both diazoxide and octreotide are capable of inducing β-cell rest. In a recent study we found that a 3-month period of supplementary treatment with diazoxide was capable of improving the endogenous production of insulin in patients with new-onset autoimmune diabetes (8). Based on the present findings, trials of octreotide in this respect would seem of value, as well as studies to determine whether the two drugs can be of additive or synergistic value.

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