Effects of Cyclosporin on Insulin and C-Peptide Secretion in Healthy Beagles

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Plasma glucose, C-peptide, and insulin responses to intravenous glucose (intravenous glucose tolerance test [IVGTT], 0.5 g/kg), glucagon (1 mg i.v.), and oral glucose (oral glucose tolerance test [OGTT], 1 g/kg) were assessed in six normal beagles before, during, and 1 and 4 mo after the administration of cyclosporin A (CsA) in doses previously shown to be required for uniform prevention of canine islet-allograft rejection (20 mg/kg; mean trough radioimmunoassay serum levels ≥500 ng/ml). Insulin secretion in response to intravenous glucose and glucagon was significantly inhibited during the administration of CsA (areas under insulin-response curves, pmol · min^{-1} · L^{-1}; IVGTT, pre-CsA, 11,127 ± 1285; during CsA, 5954 ± 1147, $P < .05$; glucagon tolerance test, pre-CsA, 18,617 ± 2807; during CsA, 4401 ± 486, $P < .05$ vs. pretreatment levels). These secretory defects persisted 4 mo after CsA was discontinued (IVGTT, 4358 ± 659; glucagon tolerance test, 10,567 ± 2479, $P < .05$). C-peptide responses paralleled these changes. Plasma glucose disposal in response to these secretagogues, however, returned to normal 1 mo after discontinuation of CsA. In contrast to the findings for IVGTT and glucagon, insulin-response curves to OGTT were not statistically different during CsA administration. We conclude that, although glucose disappearance rates are normal after discontinuation of the CsA administration, CsA causes irreversible impairment in islet secretory responses detectable with IVGTT and glucagon but not with OGTT. These results suggest that short-term CsA in doses required to prevent islet-allograft rejection in dogs can result in permanent loss of functionally competent β-cells. *Diabetes* 38:698–703, 1989

Glucose 1 mM = 18 mg/dl	Insulin 1 pM = 0.139 μU/ml

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Cyclosporin A (CsA) has attained a deserved reputation as one of the most effective immunosuppressants in experimental and clinical pancreatic transplantation (1,2). CsA is also being used in several studies attempting to halt the progression of immune-mediated pancreatic islet destruction in people with recent-onset insulin-dependent diabetes mellitus (3,4). However, pancreatic β-cell function was reported to be diminished in CsA-treated human recipients of pancreas (5,6) and kidney (7,8) allografts, and recent work in CsA-treated dogs that received segmental pancreatic autotransplants seems to corroborate these findings (9). Also, in dogs with islet allografts that led to reversal of spontaneous or pancreatectomy-induced diabetes, immunosuppression with CsA was associated over time with substantial decreases in glucose-mediated insulin release (10). Because these findings in large animals were generally demonstrated only in recipients of grafted tissues, we attempted to determine whether CsA interferes with pancreatic islet β-cell function in healthy beagles during and 30 and 120 days after the continuous administration of CsA for ~1 mo. Because these dogs had no metabolic disorders and could therefore be evaluated solely for the effect of the drug being investigated, they provided a more stringent model to study the effects of CsA on islet cell function in large animals in vivo.

MATERIALS AND METHODS

Animals. Six 12 ± 1–mo-old (mean ± SD) laboratory-bred healthy beagles (3 males and 3 females not in estrus) weighing 8–11 kg (mean wt 9.7 kg) were studied. Complete blood counts and biochemical-panel screening tests were conducted prior to entry into the study and monthly thereafter. The dogs were fed kibbled commercial dog food, and water was available ad libitum.

Study design. Before receiving CsA, each dog received three challenge tests. Intravenous glucose tolerance tests (IVGTTs), oral glucose tolerance tests (OGTTs), and intravenous glucagon tolerance tests were separated by 2–14

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days. Testing with each secretagogue did not follow a fixed order or any preselected sequence.

After each dog had undergone each secretagogue test, CsA in olive oil was administered once daily at an initial dose of 20 mg · kg^{-1} · day^{-1} i.m. The CsA doses (15–25 mg · kg^{-1} · day^{-1}) were adjusted as needed to sustain serum trough levels (24 h after the last dose) of 400–800 ng/ml (11). Beginning on the 25th day of CsA therapy, each dog was retested with each of the three secretagogues. After completion of the secretagogue tests, CsA administration was discontinued. No dog received CsA for <33 days or >40 days. Thirty and 120 days after discontinuing CsA, testing with each of the secretagogues was again carried out on each dog.

All secretagogue tests were conducted in a quiet room between 0800 and 0900 after a 16–17-h fast. Blood samples were obtained via a Silastic catheter in the cephalic vein. The IVGTT consisted of administering 50% glucose in saline (500 mg/kg body wt) for 2–3 min in the contralateral cephalic vein (12). Blood samples were taken just before and at 5, 10, 15, 20, 30, and 60 min after initiation of the infusion. The OGTT consisted of administering 50% glucose in water (1 g/kg) for 2–3 min (13). The solution was slowly deposited in the back of each dog's mouth, and they voluntarily swallowed. Blood samples were obtained just before and 5, 10, 15, 20, 30, 60, 90, 120, 150, and 180 min after the beginning of glucose administration. The glucagon tolerance test consisted of administration of 1 mg of glucagon i.v. (Lilly, Indianapolis, IN) for 2–3 min. Blood samples were taken just before and 3, 5, 10, 20, 30, and 60 min after beginning the infusion (14,15).

Sample collection. The blood samples were placed into tubes on ice containing 500 KIU/ml Trasylol and 1.2 mg/ml EDTA until the plasma was separated. After centrifugation, the portions of plasma for insulin and C-peptide analysis were stored at −70°C until assayed. The plasma glucose concentrations were determined immediately. After the initial 3 days of CsA treatment, daily serum CsA trough concentrations were determined from blood samples obtained immediately before administration of the next dose of CsA.

Analytical techniques and data analysis. Plasma glucose concentrations were determined with a glucose analyzer (Beckman, Fullerton, CA). Plasma insulin and C-peptide concentrations were measured with previously described radioimmunoassays (RIAs; 16,17). The plasma glucose, insulin, and C-peptide concentrations were all determined in duplicate. Monocomponent porcine insulin and purified canine C-peptide were used as standards in the insulin and C-peptide assays, respectively. The areas under the glucose-, insulin-, and C-peptide–response curves were computed in response to oral glucose (0–180 min) and intravenous glucagon and glucose (0–60 min). *K* values were calculated from IVGTT results, according to standard methods (18). Serum CsA concentrations were determined with an RIA kit with a polyvalent sheep anti-CsA serum (Sandoz, Basel). Serum was separated at 4°C after the samples were stored for 1 h at room temperature.

The data were analyzed by repeated-measures analysis of variance. The significance of differences between group means was evaluated by the Student-Newman-Keuls test (18a). All results were expressed as means ± SE, and $P < .05$ was considered significant.

RESULTS

Body weights remained unchanged during the study. Significant reduction in erythrocyte counts, hemoglobin, and hematocrit were noted in all dogs studied while on CsA. A significant elevation in the total serum protein concentration and declines in serum albumin and triglyceride concentrations were also observed in the chemistry profiles. These abnormalities were corrected after CsA was discontinued. We observed similar abnormalities in dogs with islet allografts treated with CsA (19). CsA treatment altered the IVGTTs (Fig. 1) and resulted in significantly higher plasma glucose concentrations at 5, 10, 15, 20, and 30 min ($P < .05$) and significantly lower *K* values (4.5%/min pre-CsA vs.

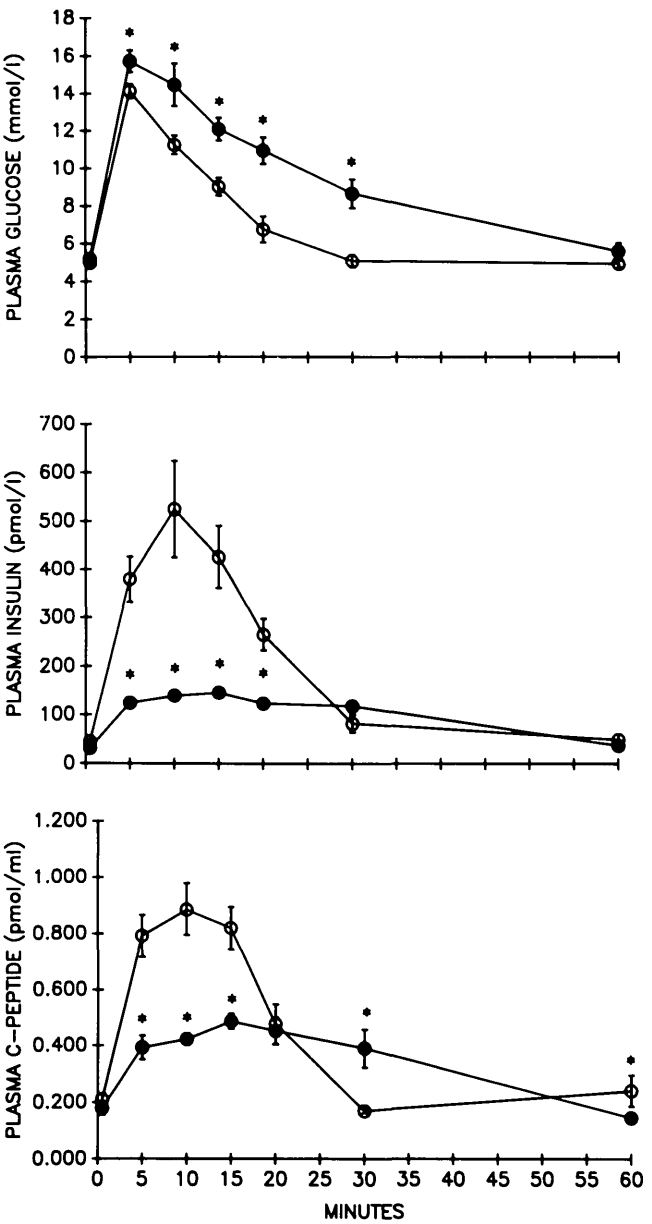

FIG. 1. Plasma glucose level and plasma insulin and C-peptide responses to i.v. glucose (0.5 g/kg) in normal beagles ($n = 6$) before cyclosporin A treatment (pre-CsA, ○) and during CsA treatment (●, 20 mg/kg for 33–40 days). Plasma insulin and C-peptide responses significantly decreased at 5, 10, 15, and 20 min and 5, 10, and 15 min, respectively, but C-peptide responses increased at 30 min during CsA treatment. Plasma glucose significantly increased at 5, 10, 15, 20, and 30 min. Values are means ± SE. *$P < .05$ pre-CsA versus during CsA.

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TABLE 1
Areas under intravenous glucose-, glucagon-, and oral glucose-response curves during and after administration of cyclosporin A (CsA) to beagles

Tolerance test condition	Glucose (mmol · min^{-1} · L^{-1})	Insulin (pmol · min^{-1} · L^{-1})	C-peptide (pmol · min^{-1} · Ml^{-1})
Intravenous glucose			
Control	410 ± 16	11,127 ± 1285	23.6 ± 1.2
During CsA	564 ± 35*	5954 ± 1147*	20.4 ± 1.7†
1 mo after CsA	440 ± 25†	5550 ± 808*	18.5 ± 3.2†
4 mo after CsA	378 ± 7†	4358 ± 659*	14.3 ± 1.4*
Intravenous glucagon			
Control	552 ± 21	18,617 ± 2807	30.4 ± 2.2
During CsA	816 ± 48*	4401 ± 486*	12.6 ± 1.5*
1 mo after CsA	561 ± 22†	10,726 ± 3299*	22.2 ± 2.5*
4 mo after CsA	531 ± 45†	10,567 ± 2479*	18.9 ± 2.0*
Oral glucose			
Control	983 ± 36	15,827 ± 1842	57.6 ± 8.3
During CsA	1178 ± 77*	16,748 ± 5191†	67.4 ± 9.2†
1 mo after CsA	1064 ± 31†	10,979 ± 1883†	56.0 ± 7.5†
4 mo after CsA	1023 ± 29†	16,085 ± 2881†	44.8 ± 4.7†

Values are means ± SE. *P* value compares mean ± SE of experimental observation with mean ± SE of control for each secretagogue. CsA dose was 20 mg/kg.
*$P < .05$, †NS, vs. control.

2.33%/min during CsA, $P < .05$). Insulin concentrations at 5, 10, 15, and 20 min, and C-peptide concentrations at 5, 10, and 15 min were significantly ($P < .05$) depressed, compared with the IVGTTs before administration of CsA (Fig. 1). The mean C-peptide concentration at 30 min was, however, significantly elevated ($P < .05$). The areas under the glucose-response curve were significantly increased, and the areas under the insulin-response curve were significantly depressed ($P < .05$) in dogs receiving CsA, compared with the areas under the curves before administration of CsA (Table 1).

K values and plasma glucose concentrations in response to intravenous glucose were normal 4 mo after discontinuation of CsA ($K = -4.5$%/min pre-CsA vs. -5.8%/min; *P*, NS), but serum insulin and C-peptide responses remained significantly depressed 5, 10, 15, and 20 min and 0, 10, 15, 30, and 60 min ($P < .05$), respectively, after intravenous glucose (Fig. 2). The areas under the insulin-response and C-peptide–response curves paralleled these changes (Table 1).

The intravenous glucagon tolerance tests evaluated during CsA treatment resulted in significantly higher ($P < .05$) plasma glucose concentrations at the 20-, 30-, and 60-min samplings (Fig. 3). By contrast, insulin and C-peptide concentrations were significantly decreased ($P < .05$) at 0, 3, 5, 10, 20, and 30 min after intravenous glucagon, but both measurements were significantly increased ($P < .05$) at the 60-min sampling (Fig. 3). During CsA treatment, the area under the glucose curve was significantly increased ($P < .05$), and areas under the insulin- and C-peptide–response curves were significantly decreased ($P < .05$; Table 1). The concentrations and areas under the glucose-response curves were normal 4 mo after discontinuation of CsA, but decreases in insulin and C-peptide concentrations were still detected 20 and 30 min and 0, 10, 20, and 30 min, respectively, after intravenous glucagon (Fig. 4). The areas under the insulin- and C-peptide–response curves to intravenous glucagon were also significantly decreased at 1 and 4 mo after discontinuation of CsA (Table 1).

The glucose, insulin, and C-peptide responses to oral glu-

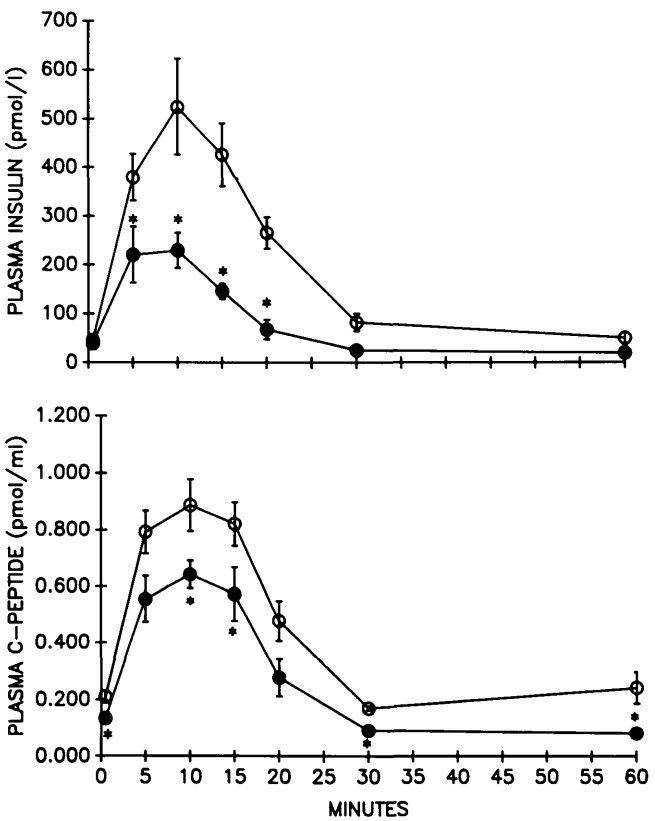

FIG. 2. Plasma insulin and C-peptide responses to i.v. glucose (0.5 g/kg) in normal beagles ($n = 6$) before cyclosporin A treatment (pre-CsA, ○) and 4 mo after CsA treatment (●). Plasma insulin and C-peptide responses were still significantly decreased at 5, 10, 15, and 20 min and 0, 10, 15, 30, and 60 min, respectively. Values are means ± SE. *$P < .05$ pre-CsA versus after CsA.

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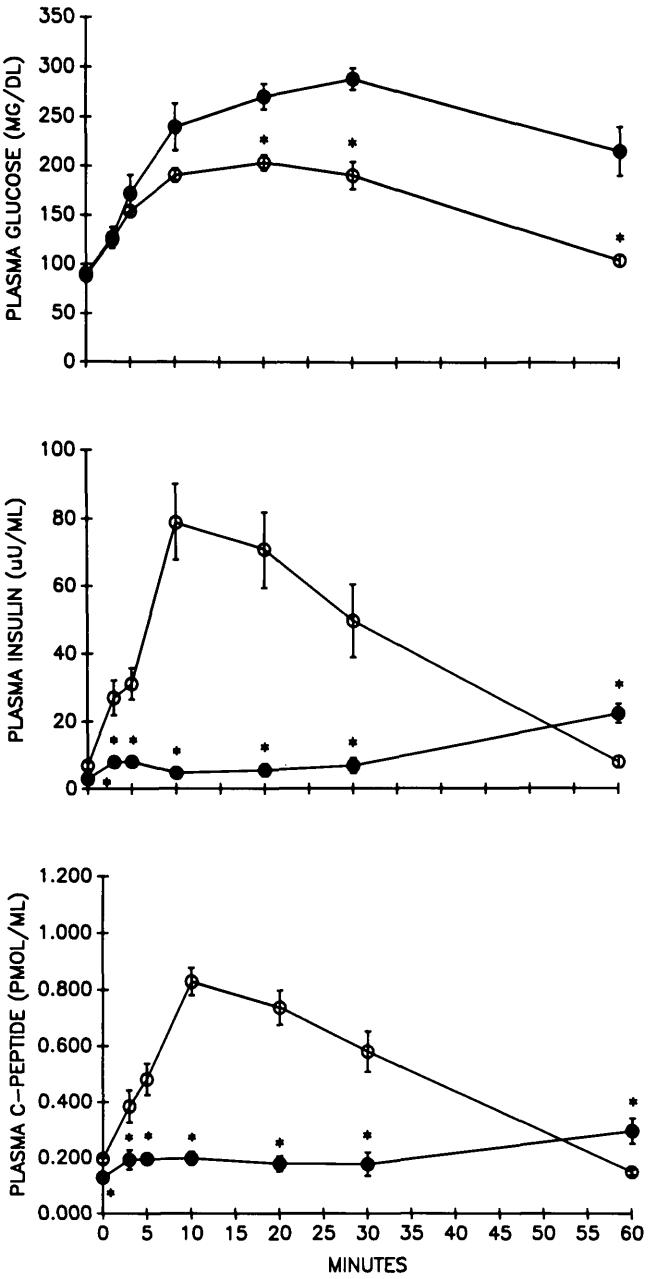

FIG. 3. Plasma glucose level and plasma insulin and C-peptide responses to i.v. glucagon (1 mg) in normal beagles (n = 6) before cyclosporin A treatment (pre-CsA, ○) and during CsA treatment (●, 20 mg/kg for 33–40 days). Plasma insulin and C-peptide responses significantly decreased at 0, 3, 5, 10, 20, and 30 min and significantly increased at 60 min. Plasma glucose responses increased at 20, 30, and 60 min. Values are means ± SE. *P < .05 pre-CsA versus during CsA.

cose administered before, during, and 1 mo after discontinuation of CsA are shown in Figure 5. The mean plasma glucose was higher 30 and 60 min after oral glucose during CsA therapy (9.62 ± 0.90 mM; 8.9 ± 0.8 mM vs. 6.65 ± 0.4 mM; 5.92 ± 0.7 mM, respectively; P < .05). These changes resulted in a greater area under the glucose-response curves (983 ± 36 pmol · min^{-1} · L^{-1} pre-CsA vs. 1178 ± 77 pmol · min^{-1} · L^{-1} during CsA), but unlike the findings with intravenous glucose and glucagon, no significant differences were observed in the insulin- and C-peptide–response curves during administration of CsA. Moreover, 1 and 4 mo after administration of CsA, the mean plasma glucose, insulin, and C-peptide responses and the mean areas under the glucose-, insulin-, and C-peptide–response curves were not significantly different from pre-CsA control levels.

Serum CsA trough concentrations. The mean serum CsA trough concentration during CsA administration was 708 ± 130 ng/ml.

DISCUSSION

We observed in a large animal, as others have observed in rodents, that CsA can result in inhibition of insulin secretory responses from the intact, normal pancreas (20–24). Previously, van Schilfgaarde et al. (9) also observed that insulin release to intravenous glucose was inhibited during administration of CsA in dogs with segmental pancreas autografts. However, in contrast to their findings, the defect in secretory responses to intravenous glucose and glucagon (tested only in this study) was only partially reversible after CsA was discontinued (Table 1). Thus, doses of CsA required to prevent islet-allograft rejection may result in irreversible deterioration in β-cell function (11,25). In addition, we observed the reappearance of fasting hyperglycemia in pancreatectomized beagles with established intrahepatic islet autografts during the administration of intramuscular CsA for 1 mo (data not shown).

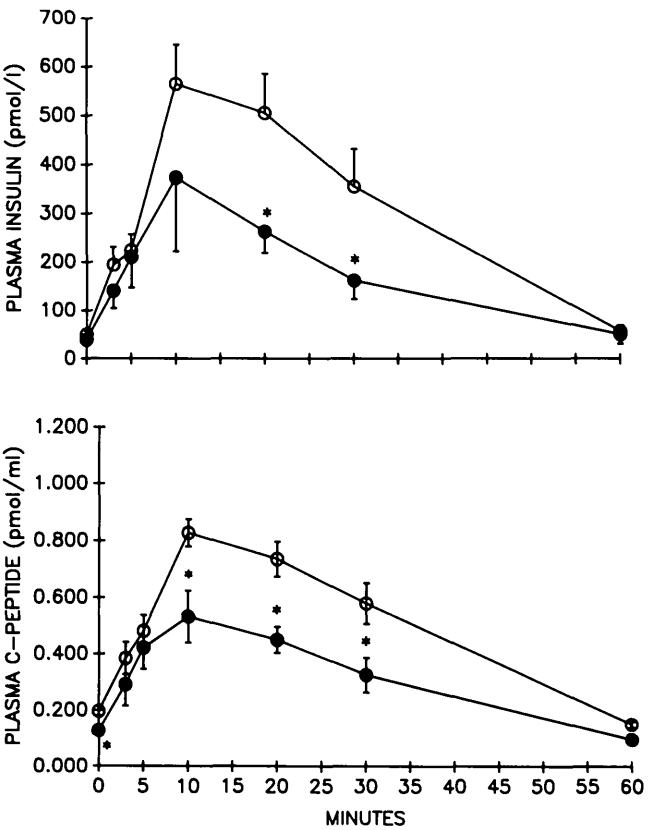

FIG. 4. Plasma insulin and C-peptide responses to i.v. glucagon (1 mg) in normal beagles (n = 6) before cyclosporin A treatment (pre-CsA, ○) and 4 mo after CsA treatment (●). Plasma insulin and C-peptide responses were still significantly decreased at 20 and 30 min and 0, 10, 20, and 30 min respectively. Values are means ± SE. *P < .05 pre-CsA versus after CsA.

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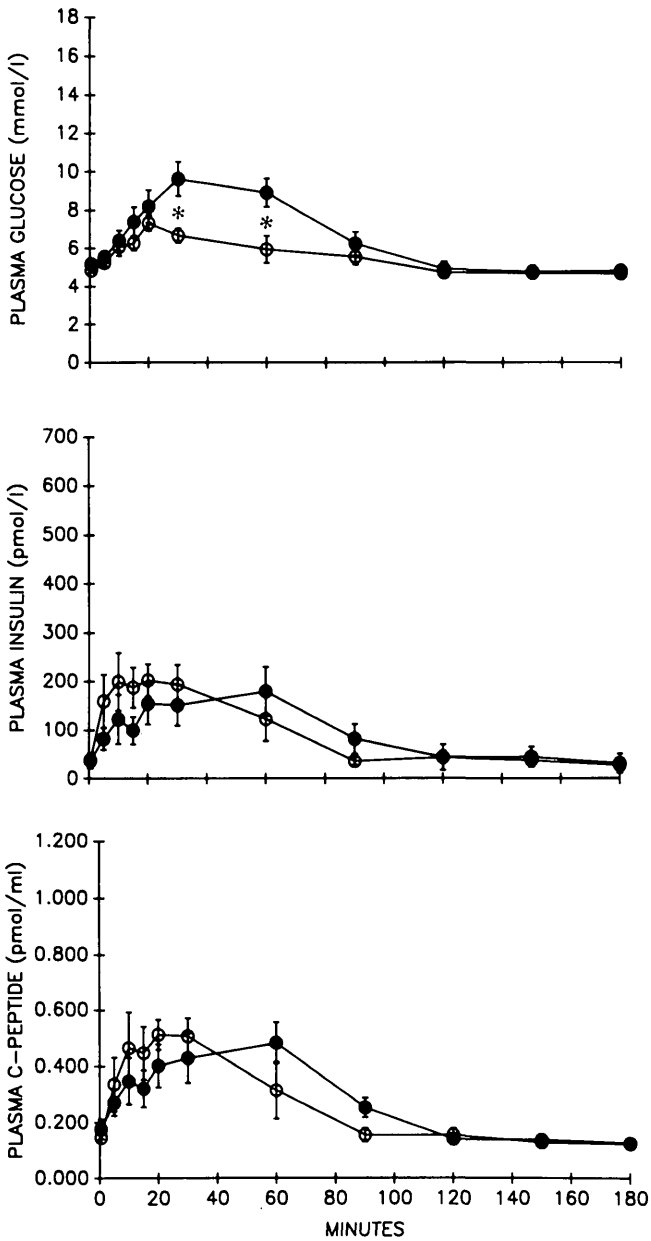

FIG. 5. Plasma glucose level and plasma insulin and C-peptide responses to oral glucose (1 g/kg) in normal beagles (n = 6) before cyclosporin A treatment (pre-CsA, ○) and during CsA treatment (●, 20 mg/kg for 33–40 days). Plasma glucose responses increased at 30 and 60 min. No significant differences were observed in insulin- and C-peptide–response curves. Values are means ± SE. *P < .05 pre-CsA versus during CsA.

Thus, the evidence seems compelling that administration of CsA can irreversibly impair islet cell function. Our evidence in support of this conclusion needs to be interpreted, however, with a degree of caution, because we did not serially study age-matched normal dogs that were administered injections of CsA-free diluent.

The persistence of a significant reduction in insulin secretion to intravenous glucose and glucagon 4 mo after CsA was discontinued is a unique finding. Others have also studied the reversibility of the inhibitory effects of CsA in vivo and in vitro. In vitro studies have shown that the inhibitory effects of CsA persisted 16 and 48 h after removal of the drug in a hamster β-cell line (HIT cells) and in human islets, respectively (26,27). The inhibitory effects of CsA can persist 2–8 wk after discontinuing oral administration of the agent to rats (21,23,24). Our results corroborate the findings of others and extend the duration of the inhibitory effects of CsA.

The long-term persistence of the inhibitory effects of CsA may merely reflect that at high doses, there is an irreversible loss of functioning β-cells due to direct cytotoxic effects of the drug on islet β-cells (28). This certainly would be consistent with the apparent induction of failure of islet autografts to sustain fasting euglycemia in pancreatectomized animals as mentioned earlier. Alternatively, although plasma levels of CsA disappear fairly rapidly after the agent is discontinued, tissue levels of this lipophilic drug have not been carefully assessed after CsA therapy is interrupted (11,25). We observed two seemingly opposing residual effects after discontinuation of high-dose CsA, namely, significant reductions in insulin responses to intravenous glucose and glucagon that are not associated with delayed plasma glucose disappearance. These residual effects suggest that withdrawal of the drug results in reversal of a block in insulin action so that a state of enhanced sensitivity to insulin may exist in association with persistence of a defect in insulin secretion. Yale et al. (21,29) have recently detailed similar observations in CsA-treated rats. These effects may reflect the continuous presence of CsA in specific tissue, rather than a residual effect of previous exposure to the drug. CsA, for example, seems to concentrate in the pancreas (30), and the effects of the drug on the prolactin receptor (31,32) suggest that it could have effects on other related receptors, including the insulin receptor.

As the use and indications for CsA administration increase, these and other actions of CsA will come under even closer scrutiny.

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