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Effect of FK 506 on Human Pancreatic Islets Following Renal Subcapsular Transplantation in Diabetic Nude Mice

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Posttransplant hyperglycemia is a well-recognized side effect of most standard immunosuppressive drugs including prednisone[1] and cyclosporine (CyA),[2–4] which are known to be diabetogenic in humans. Similar effects have been ascribed to FK 506 in both experimental[5,6] and clinical studies.[7] The aim of this study was to test the in vivo effect of FK 506 on human pancreatic islets.

MATERIALS AND METHODS

Human islets were prepared.[8,9] One week after human islet transplantation the animals were divided into four groups. In group 1 (n = 10), the animals received one injection of 0.5 mL of cremaphor-ethanol-saline (without FK 506) intraperitoneally (IP) daily for 1 week. In group 2 (n = 5), the animals were treated by daily IP injection of 0.3 mg/kg FK 506, while in groups 3 (n = 5) and 4 (n = 5) the daily injections were 1 and 3 mg/kg FK 506, respectively.

Fifteen days after islet transplantation, the animals underwent IP glucose tolerance test (IPGTT).[10]

RESULTS AND DISCUSSION

IP administration of FK 506 for 1 week at a dose of 0.3 mg/kg/d did not produce any significant alteration of glucose disappearance after IP administration of glucose. Higher doses of FK 506 produced a significant delay in plasma glucose disappearance. In groups 3 and 4. 2 of 10 animals demonstrated hyperglycemia before IPGTT (fasting plasma glucose > 200 mg/dL). In these animals, the presence of fasting hyperglycemia despite normal levels of human C-peptide indicated that peripheral insulin resistance could be responsible for the hyperglycemic effect of FK 506. Nevertheless, at high dose treatment insulin secretion appears to be impaired as well. Furthermore, 5 of 10 animals remained hyperglycemic 1 hour after IP glucose injection. Human C-peptide levels following IPGTT indicated that abnormal glucose disappearance in group 4 was associated with an initial impairment of insulin secretion from the engrafted islets. In fact, 15 minutes after glucose injection a decrease in human C-peptide levels was observed in group 4, in contrast to the control groups in which a twofold increase in C-peptide was observed. The difference in C-peptide levels between the two groups was statistically significant only at the 15 minute level ($P < .028$).

Histologic studies on the renal subcapsular islets indicated that human islets were present in the renal subcapsular space of all transplanted animals. Nevertheless, in the two animals (one

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in group 3 and one in group 4) that were hyperglycemic, the beta cells appeared degranulated. In the remaining animals the human islets appeared well preserved with no significant difference between FK 506-treated and control animals. In group 1 (control) a nephrectomy of the kidneys bearing the grafts produced a rapid return to the diabetic state, indicating that the human islets transplanted were responsible for the maintenance of normoglycemia.

This study indicates that FK 506 did not produce significant alteration of glucose homeostasis in animals treated with a dose of 0.3 mg/kg/d for 7 days. Nevertheless, the effect of the drug on insulin secretion and glucose disappearance after IP glucose have been observed at higher dosages. Although these levels are significantly higher than the therapeutic levels in current use in patients, the potential accumulation during chronic treatment with the agent in the pancreas, like CyA, may induce islet secretory defects even at therapeutic levels.

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