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Effects of cyclosporin A on the blood flow of the native and transplanted rat pancreas and duodenum

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Abstract. The aim of the present study was to evaluate the effects of cyclosporin A (CyA) on the blood perfusion of the transplanted pancreas. For this purpose syngeneic pancreaticoduodenal transplantations were performed in Wistar-Furth rats. After nephrectomy the graft was anastomosed using a nonsuturing cuff technique to the left renal vessels. Beginning 7 days after transplantation and then continuing for 2 weeks, CyA (15 mg/kg body weight) or vehicle was given p.o. once daily, 6 days a week. The serum CyA concentrations were greater than 600 ng/ml at all points in time tested. Intraperitoneal glucose tolerance tests were normal in CyA-treated animals after 12 days, but the pancreatic insulin concentration was decreased to the same extent in the native and transplanted pancreas. A microsphere technique was used to measure the blood perfusion of the pancreaticoduodenal graft, the native pancreas and duodenum, and remaining kidney 14 days after starting the CyA treatment. The renal blood flow was markedly decreased by CyA when compared with the control animals. In rats given vehicle alone, pancreatic, islet, and duodenal blood flows were higher in the graft than in the corresponding native organs. However, in rats given CyA, hyperperfusion of the graft was not observed. We conclude that the administration of CyA prevents the transplantation-induced blood flow increase seen in pancreaticoduodenal grafts of vehicle-treated rats. These observations may reflect graft denervation.

Key words: Pancreas transplantation, rat – Pancreas transplantation, blood flow – Cyclosporin, pancreas transplantation

Introduction

Since its introduction, cyclosporin A (CyA) [6], in combination with azathioprine and prednisolone, has been the most commonly used immunosuppressant after solid organ transplantation [39]. CyA may also be of potential value in the treatment of several autoimmune disorders, such as diabetes mellitus [31], iridocyclitis [24], and thyroiditis [35]. Major toxic effects involving the kidneys [19, 29], liver [8], and pancreas [9, 41] have, however, precluded a more common clinical use. The endocrine pancreas is more sensitive to the toxic effects of CyA than the exocrine part [21], and treatment with CyA leads to a marked degranulation and functional impairment of the pancreatic islets both in vitro [2] and in vivo [9, 11, 41]. Recently, it has been suggested that CyA decreases the pancreatic blood perfusion in acute experiments [16], a finding similar to that observed in the kidney [20, 22, 30].

The present study was performed to elucidate what effects CyA may have on syngeneic pancreaticoduodenal grafts in rats. In order to compare its effects on a transplanted pancreas with those on the intact gland, the implantations were performed on normoglycemic animals, i.e., rats with a normal native pancreas. After 2 weeks of CyA treatment, the glucose tolerance of the animals was investigated. In addition, the pancreatic insulin concentration and the blood perfusion of the whole pancreas and the islets in both the native and transplanted pancreas were measured.

Materials and methods

Animals

Inbred male Wistar-Furth rats (ALAB, Sollentuna, Sweden) weighing approximately 300 g were used in all of the experiments. The animals had free access to tap water and pelleted food (Type R43; Ewos, Södertälje, Sweden) throughout the experiments. After the transplantation the animals were housed one per cage in a room with a 12-h light/dark cycle at a constant temperature (22 °C).

Pancreaticoduodenal transplantation

This procedure has been described in detail elsewhere [15]. Briefly, the donor was anesthetized with an intraperitoneal injection of chloral hydrate (360 mg/kg body weight) and placed on a heated operating table. The whole pancreas, together with approximately 1 g of

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the small intestine, was dissected free from surrounding tissues. Via a catheter in the aorta, the preparation was flushed with 5–7 ml of cold (4 °C) University of Wisconsin (UW) solution (Belzer UW-CSS, Du Pont Pharmaceuticals, Wilmington, Del., USA) [37] at a pressure of approximately 100 cm H_2O. The warm ischemia time was less than 2 min. The graft was then removed from the animal, together with approximately 1 cm of the aorta, which contained the two arterial vessels to the gland, and stored at 4 °C for 1.5–2 h (cold ischemia time) before being implanted in the recipient.

The recipients were also anesthetized with chloral hydrate and placed on a heated operating table. The left kidney was removed and the pancreaticoduodenal graft was anastomosed to the renal vessels using a nonsuturing cuff technique as previously described in detail [15, 25]. The graft small intestine was sutured end-to-side to a loop of the colon of the recipient with approximately 10 sutures of 7-0 silk. After closure of the abdominal wound, the animals were injected subcutaneously with 10 mg doxycycline (Idocyclin; AB Leo, Malmö, Sweden) and were observed until fully recovered from anesthesia.

Treatment with cyclosporin A

All animals were allowed to recover for 7 days after the transplantation since rats given CyA immediately after transplantation developed severe infections (unpublished observation). From day 8 onwards the animals were given one daily oral dose of 15 mg/kg body weight CyA (Sandimmun; Sandoz, Basel, Switzerland) dissolved in 2–2.5 ml of a fatty emulsion (Intralipid; KabiVitrum AB, Stockholm, Sweden). Control animals received the vehicle alone. This treatment was given 6 days a week for a total of 2 weeks. Approximately 0.2–0.4 ml of blood was withdrawn from the cut tip of the tail every 3rd day after starting the CyA or vehicle treatment. This blood was later analyzed for concentrations of CyA with a monoclonal antibody in a commercial radioimmunoassay kit (Sandoz, Basel, Switzerland) according to the kit instructions.

Measurements of glucose and insulin

The blood glucose concentration was measured before starting the CyA or vehicle treatment and then every 3rd day with an ExacTech blood glucose meter (Baxter Travenol Labs, Deerfield, Ill., USA) in samples collected from the cut tip of the tail. Twelve days after starting the treatment with CyA or the vehicle, some of the animals were injected intraperitoneally with a 30% (w/v) glucose solution (2 g glucose/kg body weight). Blood samples were secured immediately before the injection and 10, 30, 60, and 120 min later; they were subsequently analyzed as described above.

At the time of the blood flow measurements, 21 days after transplantation, i.e., 14 days after starting the CyA or vehicle treatment, blood samples were collected from arterial catheters and later analyzed for glucose concentrations using an automated glucose oxidase techique (Glucose Analyzer 2; Beckman Instruments, Fullerton, Calif., USA) and for insulin concentrations with radioimmunoassay. After performing the blood flow measurements, approximately 20 mg (wet weight) from the caudal region of both the native and transplanted pancreas were removed and immediately frozen. The pancreatic pieces were then analyzed for their insulin concentration as previously described [14].

Blood flow measurements

Fourteen days after starting treatment with either CyA or the vehicle, i.e., 21 days after transplantation, the animals were anesthetized with an intraperitoneal injection of thiobutabarbital sodium (110 mg/kg body weight; Inactin Byk; Byk Gulden, Konstanz, FRG), heparinized, and placed on a heated operating table. Mean arterial blood pressure and body temperature were monitored throughout the experiments. Blood flows of the whole native and transplanted pancreases, the islets in both glands, the native and transplanted intestines, and the kidney were then measured using a microsphere technique, as previously described in detail [13, 15]. Briefly, arterial polyethylene catheters were placed at the aortic root via the right carotid artery and in the lower part of the abdominal aorta via the left femoral artery. After allowing the blood pressure to stabilize for at least 20 min, $1.5–2.0 \times 10^5$ nonradioactive microspheres (diameter 11.1 ± 0.2 μm; mean ± SD; NEN Chemicals, Boston, Mass., USA) were injected for 10 s through the catheter into the carotid artery. Starting 5 s before this injection and continuing for a total of 60 s, arterial blood was allowed to flow freely (approximate rate 0.50 ml/min) from the catheter in the femoral artery into a preweighed tube. The withdrawal rate was then calculated by weighing the sample. Both the native and transplanted pancreas and the duodenum and kidney were removed, blotted, and weighed. The microsphere contents of the organs and the blood reference sample were then counted in a microscope equipped with both light and dark field illumination, as previously described [13]. The blood flow values could then be calculated according to the formula: $Qorg = Qref \times Norg/Nref$, where Qorg is the organ blood flow (ml/min), Qref is the withdrawal rate of the reference sample (ml/min), Norg is the number of microspheres in the organ, and Nref is the number of microspheres in the reference sample.

Morphological examinations

Small pieces (approximately 10% of the whole organ) were removed from both the native and transplanted pancreas and duodenum, respectively, after the blood flow measurements. These pieces were subsequently fixed in Bouin's solution, dehydrated, and embedded in paraffin. Seven-micrometer-thick sections were then stained with hematoxylin and eosin.

Statistical calculations

All values are given as means ± SEM. Probabilities (P) of chance differences between the values for the native and transplanted organs within the same animals were calculated with Student's paired, two-tailed *t*-test, while comparisons between the values for CyA- and vehicle-treated rats were calculated with Student's unpaired, two-tailed *t*-test.

Results

Of 23 transplanted animals, 3 were excluded from the study (1 CyA-treated and 2 control rats) due to excessive fibrosis of the pancreatic gland. The vehicle-treated controls increased significantly in body weight during this time period (from 308 ± 7 to 323 ± 6 g; $P < 0.05$; $n = 9$), whilst the animals given CyA maintained their body weight (323 ± 5 vs 318 ± 7 g; $n = 11$). The serum concentrations of CyA were high at all points in time tested and were never below 600 ng/ml (988 ± 63 ng/ml; $n = 58$).

Glucose and insulin concentrations

The serum glucose and insulin concentrations of the CyA-treated rats were similar to those of the control animals at the time of the blood flow measurements (Table 1). Blood glucose concentrations measured every 3rd day after transplantation were normal at all points in time (< 7 mM) and did not differ between the CyA and control rats (data not shown). Intraperitoneal glucose tolerance tests performed 12 days after initiation of the CyA treat-

Table 1. Mean arterial blood pressure, serum glucose and insulin concentrations, and pancreatic insulin concentrations of the native and transplanted pancreas, respectively, in rats transplanted with a syngeneic pancreaticoduodenal graft 21 days earlier. The animals had been given cyclosporin A (15 mg/kg body weight p.o.) or vehicle alone for 14 days before the measurements. All values represent means ± SEM. * $P < 0.05$ when compared with the vehicle-treated rats

Treatment given No. of animals	Vehicle 9	Cyclosporin A 11
Mean arterial blood pressure (mm Hg)	116 ± 6	110 ± 6
Serum glucose concentration (m*M*)	8.2 ± 0.7	8.3 ± 0.5
Serum insulin concentration (ng/ml)	1.39 ± 0.29	1.43 ± 0.21
Pancreatic insulin concentration (ng/mg wet weight)		
Native pancreas	103 ± 14	79 ± 12*
Transplanted pancreas	114 ± 21	88 ± 13*

Table 2. Whole pancreatic blood flow, islet blood flow, and small intestinal blood flow in the native and transplanted (tx) pancreas and duodenum, respectively, and renal blood flow in rats transplanted with a syngeneic pancreaticoduodenal graft 21 days earlier. The animals had been given cyclosporin A (15 mg/kg body weight p.o.) or vehicle alone for 14 days before the measurements. All values represent means ± SEM. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared with the vehicle-treated rats

Treatment given No. of animals	Vehicle 9	Cyclosporin A 11
Renal blood flow (ml/min × g kidney)	4.30 ± 0.48	2.20 ± 0.26***
Pancreatic blood flow (ml/min × g pancreas)		
Native pancreas	0.68 ± 0.10	0.75 ± 0.06
Tx pancreas	1.01 ± 0.21	0.82 ± 0.11
Islet blood flow (μl/min × g pancreas)		
Native pancreas	45 ± 7	47 ± 6
Tx pancreas	88 ± 21	45 ± 6*
Islet blood flow (% of pancreatic blood flow)		
Native pancreas	6.8 ± 0.8	6.2 ± 0.5
Tx pancreas	9.1 ± 0.8	5.9 ± 0.5**
Intestinal blood flow (ml/min × g intestine)		
Native intestine	0.78 ± 0.07	0.57 ± 0.09
Tx intestine	1.07 ± 0.09	0.70 ± 0.04**

ment were similar in both groups of animals (Fig. 1). The insulin concentrations of both the native and transplanted pancreas were decreased to the same degree in the CyA-treated rats as in the control animals (Table 1).

Blood flow values

The mean arterial blood pressure was similar in both groups of animals at the time of the blood flow measurements (Table 1). The renal blood flow was markedly decreased in the animals given CyA when compared to the control rats (Table 2). Not only the whole pancreatic blood flow ($P < 0.05$) but also the islet ($P < 0.05$) and duodenal blood flows ($P < 0.01$) were higher in the transplanted organs than in the native organs in the animals given only the vehicle (Table 2). However, there was no such increase in the blood perfusion of the pancreaticoduodenal graft after administration of CyA (Table 2).

Whole pancreatic blood flows of both native and transplanted pancreases did not differ between CyA-treated and control rats (Table 2). The islet blood flow was similar in the native pancreas of control and CyA rats, whereas CyA treatment caused a significant decrease in the transplanted pancreas (Table 2). These latter changes were also seen when islet blood flow was expressed as a fraction of the whole pancreatic blood flow (Table 2). CyA also caused a reduction in the flow of the transplanted, but not the native, duodenum when compared with the vehicle-treated animals.

Morphology

When examined by light microscopy, the appearance of both the native and transplanted organs was normal, with the exception of a few scattered mononuclear cells that were present in the pancreatic stroma and in the duodenal submucosa of the graft.

Discussion

Oral administration of CyA may lead to a variable absorption of the drug [38]. However, treatment with 15 mg/kg body weight CyA, as performed in the present study, produced serum concentrations of CyA known to give sufficient immunosuppression in the rat [38]. The reduced renal blood flow observed after CyA administration also shows that there was sufficient absorption of the drug [22, 30]. In contrast, CyA did not influence the whole pancreatic, islet, or duodenal blood flow in the native organs. It is not known why the susceptibility to the flow-decreasing properties of CyA between organs is different. It has, however, been suggested that CyA may interfere with calcium channels in vascular smooth muscle [23]. The addition of calcium channel blockers, such as verapamil or diltiazem, seems to prevent some of the toxic effects on the kidney by increasing the renal blood perfusion [30, 32, 36]. Interestingly, Jennings and Corry [16] observed an increased vascular resistance in the native pancreas of nontransplanted rats when giving CyA in acute experiments. This increase could, however, be prevented by the simultaneous administration of verapamil. Youngelman et al. [43], on the other hand, demonstrated an increased pancreatic blood flow in nontransplanted sheep after oral administration of CyA for 4 weeks. These discordant findings on the effects of CyA on pancreatic blood flow are likely to be due to differences in the duration of the CyA treatment and species differences. Furthermore, when CyA is given parenterally, it is dissolved in Cremophor, a castor oil derivative. This substance has vasoactive properties [1], which may also explain some of the differences referred to above.

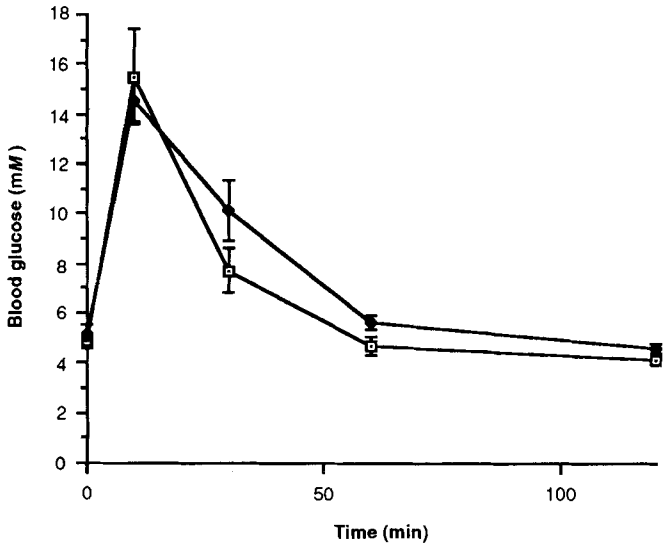

Fig. 1. Blood glucose concentrations before and at different points in time after an intraperitoneal injection of D-glucose (2 g/kg body weight). The glucose was given 12 days after transplantation in animals treated with cyclosporin A (●) or vehicle (□)

Duodenal, whole pancreatic, and islet blood flows were all higher in the graft of the vehicle-treated rats than in the corresponding native organs, thereby confirming previous results in the pancreas [15] and in other organs [12, 40]. The mechanisms behind this flow increase are unknown but may reflect graft denervation. That denervation changes the blood flow of the transplanted pancreas is supported by findings that the $beta_2$ adrenoceptor agonist terbutaline exerts its islet blood flow-decreasing properties [14] only in the innervated native pancreas and not in the denervated transplanted pancreas (unpublished observation). Administration of CyA prevented this blood flow increase in the whole pancreaticoduodenal graft, especially in the islets. It has been shown repeatedly that CyA decreases the blood flow of transplanted kidneys, but kidneys with intact innervation seem to be even more sensitive to this effect [20, 22].

The pancreaticoduodenal graft is not reinnervated 3 weeks after implantation (unpublished observation). However, both the intestines and the pancreas contain a highly developed intrinsic nervous system, with several ganglia [33, 34]. It is of interest in this context that CyA is a nonspecific alpha-adrenergic receptor antagonist, which competitively inhibits both alpha-1 and alpha-2 receptors [27]. This means that circulating and/or local adrenergic substances may exert a predominant effect on the β-adrenergic receptors, leading to a decreased islet blood flow [14]. However, since the islet blood flow was affected only in the transplanted gland, there may be a difference in sensitivity, e.g., a hypersensitivity, to adrenergic substances in grafted organs, as suggested for intraportally implanted islets [28]. It is not known if this also occurs in vascularized grafts. An alternative explanation for the CyA-induced decrease in the graft blood flow may be induced changes in arachidonic acid metabolism [5, 7, 18] or effects on the formation of endothelin-1 [4, 42]. To what extent the observed prevention of the normally observed hyperperfusion of the pancreaticoduodenal graft may be beneficial or detrimental to the ultimate function of the graft is presently unknown. Although CyA prevents hyperperfusion of the graft, it does not decrease the blood flow below that normally encountered in each respective native organ. Therefore, the blood flow impairment caused by CyA in the pancreaticoduodenal graft may be of little practical importance.

CyA is known to accumulate in the pancreas [17] and to produce glucose intolerance, both in humans [8] and in experimental animals [10, 26, 41]. We were, however, unable to detect any abnormalities in the glucose homeostasis of the animals treated for 12 days with CyA. It should be noted, however, that our rats actually had two functional pancreases, and the large excess of insulin-producing cells may have partially compensated for the toxic effects of CyA. That CyA nevertheless had a detrimental effect on the endocrine pancreas, both in the native and in the transplanted gland, was shown by the 20%–25% decrease in pancreatic insulin concentration. This has previously been shown in studies carried out both in vivo [10, 11] and in vitro [2]. Although not investigated morphometrically, islet morphology of both the native and transplanted glands seemed to be normal [3]. This may indicate that CyA in this study induced a degranulation of the B cells, but probably not cell death. The insulin concentration of the transplanted gland of these CyA-treated rats was similar to that of their native pancreas, suggesting that no preferential loss of islets in the graft had taken place. This may also indicate that the sensitivity of the islets to CyA was similar in the native and transplanted pancreas [26].

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