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The influence of cyclosporin A on the vascular permeability of the pancreatic islets and on diabetes induced by multiple low doses of streptozotocin in the mouse*

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Summary. The aim of the present study was to investigate the influence of cyclosporin A on the course of multiple low dose streptozotocin induced diabetes in mice, an animal model for human type I diabetes mellitus. C57BL/Ks mice were treated on five consecutive days with intraperitoneal injections of steptozotocin or citiric acid buffer. Thirty min before the injections the animals were given cyclosporin A (10 or 50 mg/kg body weight) or saline. Cyclosporin A did not protect against the hypoglycaemia and at the higher dose it potentiated the diabetogenic effect. Furthermore, cyclosporin A did not affect the development of insulitis when the pancreatic glands were examined by light microscopy. Using a technique for monitoring vascular permeability in vivo with the aid of the pigment Monastral Blue B, it was found that the development of diabetes was accompanied by an increased vascular leakage. Control animals treated with cyclosporin A also showed an increased islet staining with Monastral Blue B. The data indicate that cyclosporin A potentiates diabetes induced by low doses of streptozotocin. This can be attributed to a direct toxic effect of cyclosporin A on the pancretic B-cells and may also be due to an increased vascular leakage induced by cyclosporin A. The latter would allow an increased migration of inflammatory cells into the islets and the consequent release of B-cytotoxic substances.

Key words: Cyclosporin A – Diabetes – Pancreatic islets – Streptozotocin

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Introdution

The immunosuppressive drug cyclosporin A (CsA) has been shown to affect autoimmune diseases (Nussenblatt 1981; Vladutio 1983) and to prevent graft rejection after transplantation (Calne et al. 1981). In view of these effects, CsA has rapidly become one of the most commonly drugs used in clinical transplantation (Merion et al. 1984). The drug has also been administered therapeutically in attempts to prevent the progression of Type I diabetes in humans (Stiller et al. 1983; Feutren et al. 1986), since there is evidence for an autoimmune process directed against the B-cells in this disease (Nerup and Lernmark 1981). In accord with this CsA was also found to inhibit spontaneous diabetes in rodents (Laupacis et al. 1983).

However, studies in another animal model of Type I diabetes, namely the multiple low-dose streptozotocin treatment of mice (Like and Rossini 1976), have shown aggravation of the disease after CsA-treatment rather than beneficial effects (Sestier et al. 1985; Kolb et al. 1985). Further studies have demonstrated a decrease in glucose tolerance and a decrease in insulin content of the pancreas in vivo (Helmchen et al. 1984; Kojima et al. 1986; Hahn et al. 1986) and an impairment of islet B-cell function in vitro (Andersson et al. 1984).

Since these findings indicate a toxic effect of CsA on the pancreatic islets we have now studied the effects of this drug alone and in combination with multiple low-dose streptozotocin injections in mice. Serum glucose concentrations and islet morphology in the mice were examined. Furthermore, the effects of these substances were also evaluated by injections of Monastral Blue B, a dye which has been found of use in demonstrating both increased vascular permeability of the islets and ongoing B-cell destruction (Sandler and Jansson

Table 1. Serum glucose concentrations in C57BL/Ks mice before and 3–14 days after intraperitoneal injections with streptozotocin (SZ; 40 mg/kg body-weight) or citric acid buffer (0.2 ml) for up to five consecutive days. Thirty min before the injections of SZ or citric acid buffer the animals were given intraperitoneal injections of Cyclosporin A (CsA; 10 or 50 mg/kg body-weight) or saline (9 g/l; 0.2 ml)

Days after starting the treatment	Serum glucose concentration (mM)			
	Before[a]	3 days	7 days	14 days
Saline + citric acid buffer	10.3 ± 0.3 (18)	8.2 ± 0.3 (18)	7.7 ± 0.5 (12)	8.8 ± 0.3 (6)
CsA (10 mg/kg body-weight) + citric acid buffer	9.7 ± 0.3 (19)	8.1 ± 0.4 (19)	7.8 ± 0.2 (13)	8.8 ± 0.6 (7)
CsA (50 mg/kg body-weight) + citric acid buffer	8.8 ± 0.2 (23)***	6.5 ± 0.3 (23)***	6.7 ± 0.3 (15)	8.1 ± 0.5 (6)
Saline + SZ	9.9 ± 0.4 (18)	8.3 ± 0.3 (18)	13.0 ± 1.8 (12)*	21.4 ± 1.9 (6)***
CsA (10 mg/kg body-weight) + SZ	9.9 ± 0.4 (19)	8.2 ± 0.3 (19)	16.4 ± 1.0 (12)	25.8 ± 2.7 (6)
CsA (50 mg/kg body-weight) + SZ	9.1 ± 0.2 (20)	7.6 ± 0.4 (20)	21.3 ± 1.7 (12)*****	29.2 ± 1.5 (5)****

Blood samples were taken by retroorbital sinus puncture and the serum glucose concentrations were analysed by an automated glucose oxidase method

[a] This blood sample was obtained before any drugs had been given. All values are means ± SEM for the number of animals given within parenthesis

* and *** denote $P<0.05$ and $P<0.001$, respectively, when comparing with animals treated with saline + citric acid buffer. **** and ***** denote $P<0.05$ and $P<0.001$, respectively, when comparing with animals treated with saline + SZ

1985; Jansson and Sandler 1986). It was also recently suggested that enhanced vascular permeability may play a role in immune-mediated B-cell destruction (Schwab et al. 1986), and treatment with substances reduing capillary permeability was recently found to modulate streptozotocin-induced diabetes in mice (Beppu et al. 1987).

Materials and methods

Three to four months male inbred C57BL/Ks mice, originally obtained from the Jackson Laboratory, Bar Harbor, ME, USA, were used. They had free access to tap water and pelleted food (Type R3; Ewos, Södertälje, Sweden) throughout the experiments. Animals received two daily intraperitoneal injections, separated by 30 min, for 3 or 5 days. First 0.2 ml of either CsA (10 or 50 mg/kg body-weight; CsA; Sandimmun^R (50 mg/ml), Sandoz, Basel, Switzerland was generously supplied through Dr C.-G. Groth, Department of Transplantation Surgery, Huddinge Hospital, Huddinge, Sweden) diluted with saline (158 mM) or saline alone was injected. The second injection consisted of 0.2 ml of either streptozotocin (SZ; Lot 2408A, kindly provided by W.E. Dulin, Upjohn Company, Kalamazoo, MI, USA; 40 mg/kg body-weight dissolved in a citric acid buffer (10 mM; pH 4.5)) or 0.2 ml citric acid buffer alone. A total of six experimental groups thereby resulted, receiving: CsA (10 mg/kg body-weight) + SZ, CsA (10 mg/kg body-weight) + citric acid buffer, CsA (50 mg/kg body-weight) + SZ, CsA (50 mg/kg body-weight) + citric acid buffer, saline + SZ and saline + citric acid buffer, respectively.

Before starting the treatment a blood sample was obtained by puncture of retro-orbital veins and the serum glucose concentration was later analyzed using an automated glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA, USA). A second sample was taken before killing the animals on days 3, 7 or 14 after starting the treatment. After the second blood sample the animals were injected intravenously with 0.1 ml of a suspension of Monastral Blue B (3% (w/v) phthalocyanine blue pigment dissolved in saline; Sigma Chemicals, St Louis, MO, USA) and killed 1 h later. The pancreases were quickly removed, dissected free from surrounding tissues and weighed. Approximately 50% of the gland was fixed in Bouin's solution and embedded in paraffin.

Sections, 7 μm thick, were stained with eosin and haematoxylin and the islet morphology examined with the examiner being unaware of the origin of the sections. The presence of inflammatory reactions in the islets was ranked accordng to four classes as previously defined (Sandler and Andersson 1985); Class A denotes normal islet morphology; class B denotes a low degree of mononuclear cell infiltration especially in the periinsular area; class C denotes a heavy infiltration with mononuclear cells into a large number of islets and class D denotes only a few residual islets with cellular disarray and pyknotic nuclei, in the pancreatic sections.

The other half of the pancreas was weighed and treated with a freeze-thawing technique (Jansson and Hellerström 1981) to visualize the islets and the Monastral Blue B pigment. By using a stereo microscope equipped with both bright and dark field illumination, both the total number of islets with a diameter exceeding 50 μm and the number of islets labelled with Monastral Blue B could be determined as previously described in detail (Sandler and Jansson 1985; Jansson and Sandler 1986).

All numerical values are expressed as means ± SEM in the text. Groups of data were compared using Student's, unpaired t test.

Results

The animals treated with SZ, had significantly increased serum glucose concentrations on day 7 and on day 14 when compared with the control animals injected with saline and citric acid buffer (see Table 1). A further increase in the magnitude of hyperglycaemia in the SZ-injected animals simultaneously injected with CsA (50 mg/kg body weight), was observed on day 7 and on day 14 compared to animals treated with SZ and saline only. Neither dose of CsA given for five days together with citric

Table 2. Number of observed islets per pancreatic weight in C57BL/Ks mice 3–14 days after intraperitoneal injections with streptozotocin (SZ; 40 mg/kg body-weight) or citric acid buffer (0.2 ml) for up to five consecutive days. Thirty min before the injections of SZ or citric acid buffer the animals were given intraperitoneal injections of Cyclosporin A (CsA; 10 or 50 mg/kg body-weight) or saline (9 g/l; 0.2 ml)

Days after starting the treatment	Number of observed islets (islets/mg pancreas)		
	3 days	7 days	14 days
Saline + citric acid buffer	2.2 ± 0.13 (6)	2.3 ± 0.28 (6)	2.2 ± 0.21 (6)
CsA (10 mg/kg body-weight) + citric acid buffer	2.4 ± 0.36 (6)	2.6 ± 0.34 (6)	2.4 ± 0.21 (6)
CsA (50 mg/kg body-weight) + citric acid buffer	2.3 ± 0.15 (8)	0.90 ± 0.19 (9)***	2.1 ± 0.19 (6)
Saline + SZ	2.0 ± 0.22 (6)	0.35 ± 0.10 (5)***	0.05 ± 0.02 (7)***
CsA (10 mg/kg body-weight) + SZ	2.1 ± 0.27 (7)	0.13 ± 0.08 (7)	0.02 ± 0.01 (6)
CsA (50 mg/kg body-weight) + SZ	2.4 ± 0.15 (8)	0.08 ± 0.02 (7)****	0.06 ± 0.01 (5)

The pancreatic glands were weighed after killing the mice and the pancreatic islets were visualized in the pancreas by a freeze-thawing technique. Values are means ± SEM for the number of animals given within parenthesis. *** denotes $P < 0.001$ when comparing with animals treated with saline + citric acid buffer. **** denotes $P < 0.05$ when comparing with animals treated with saline + SZ

Table 3. Fraction of pigment-stained islets in the pancreas following injection of Monastral Blue B in C57BL/Ks mice 3–14 days after intraperitoneal injections with streptozoticin (SZ; 40 mg/kg body-weight) or citric acid buffer (0.2 ml) for up to five consecutive days. Thirty min before the injections of SZ or citric acid buffer the animals were given intraperitoneal injections of Cyclosporin A (CsA; 10 or 50 mg/kg body-weight) or saline (9 g/l; 0.2 ml)

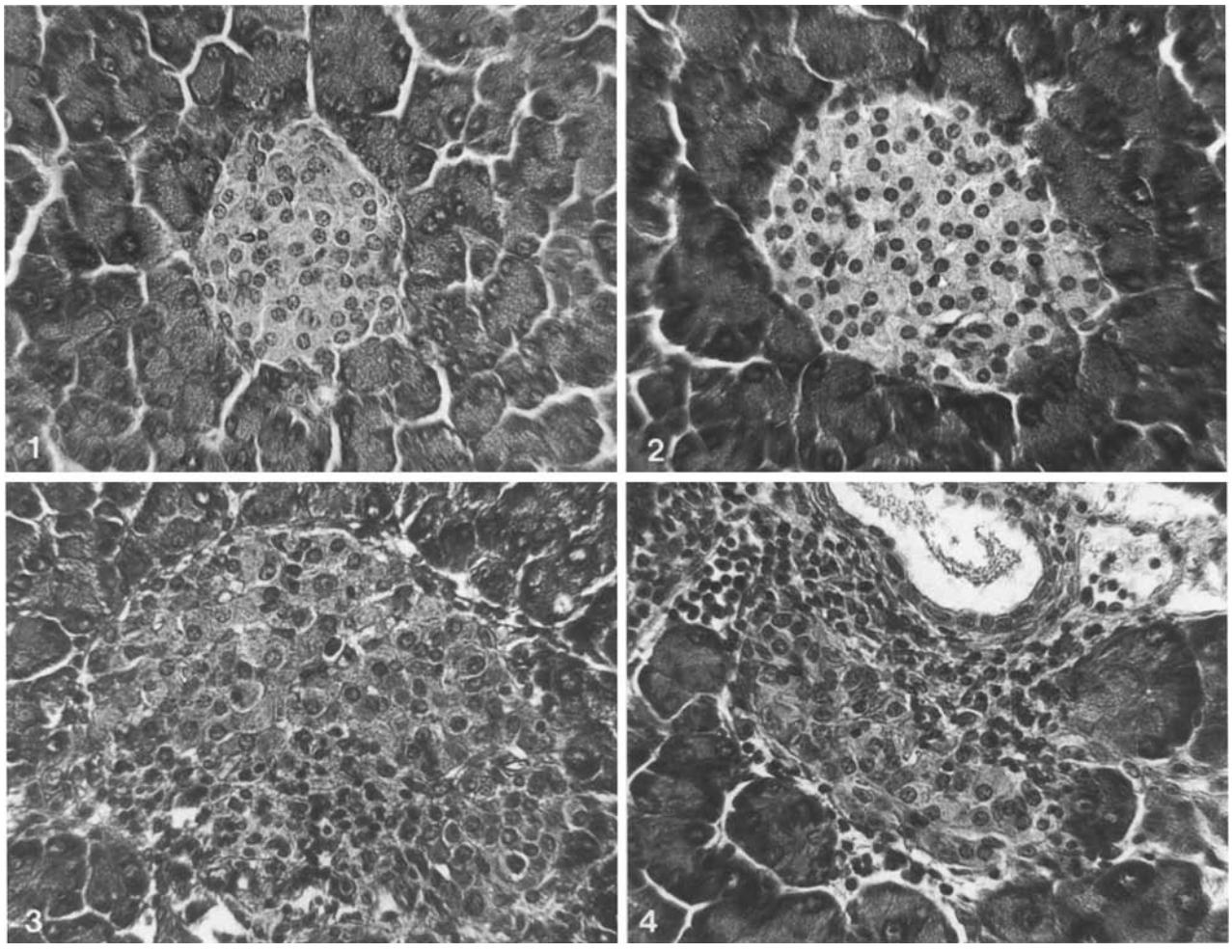
Days after starting the treatment	Percent islets staind with Monastral Blue B (%)		
	3 days	7 days	14 days
Saline + citric acid buffer	4.2 ± 1.2 (6)	0.6 ± 0.5 (6)	1.4 ± 0.6 (7)
CsA (10 mg/kg body-weight) + citric acid buffer	9.2 ± 2.1 (6)	12 ± 2.1 (6)***	14 ± 5.0 (7)***
CsA (50 mg/kg body-weight) + citric acid buffer	6.4 ± 1.4 (8)	53 ± 5.5 (9)***	4.7 ± 1.7 (6)
Saline + SZ	12 ± 2.4 (6)*	52 ± 16 (5)**	85 ± 6.3 (7)***
CsA (10 mg/kg body-weight) + SZ	4.8 ± 1.1 (7)****	76 ± 8.8 (7)	67 ± 7.4 (6)
CsA (50 mg/kg body-weight) + SZ	6.5 ± 0.8 (8)****	95 ± 4.6 (7)****	80 ± 15 (5)

Monastral Blue B was injected intravenously and the animals were killed 60 min later and the islets of the pancreas were visualized using a freeze-thawing technique. Values are means ± SEM for the number of animals given within parenthesis. *, ** and *** denote $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively, when comparing with animals treated with saline + citric acid buffer. **** denotes $P < 0.05$ when comparing with animals treated with saline + SZ

acid buffer had an effect on the serum glucose concentrations at any of the time points.

When the freeze-thawing technique for visualization of the islets was applied a rather constant number of 2–2.4 islets/mg pancreas could be observed in the animals treated with saline and citric acid buffer (Table 2). Administration of CsA at the lower dose did not influence the number of visible islets in the citric acid buffer treated animals, however, with the higher dose of CsA there was a transient reduction by approximately 60% on day 7. On day 14 the number of visible islets were again normalized in the latter group. The SZ-treated animals had a significantly decreased number of visible islets in the pancreas both on day 7 and on day 14. CsA seemed to promote the disappearance of visible islets after SZ administration. Thus, animals given the high dose of CsA + SZ showed lower values on day 7 compared to those given saline + SZ.

The fraction of islets showing labelling with Monastral Blue B was approximately 1% in the animals injected with saline and citric acid buffer, with the exception of the animals sacrificed on day 3 where about 4% of the islets were labelled (Table 3). Mice injected with CsA plus citric acid buffer showed an increased fraction of islets labelled on day 7. In the animals treated with CsA (50 mg/kg body weight) these changes were reversed after another week i.e. at day 14. A marked labelling in the exocrine tissue was also observed on days 7 and 14 in the animals treated with CsA and citric acid buffer. Three days after beginning the treatment both doses of CsA produced decreased pigment labelling of the islets in the SZ-treated mice. All SZ-treated animals, however, showed staining of a large fraction of their islets by Monastral Blue B on day 7 and 14 and CsA further potentiated this effect. Thus, on day 7 as many as 95% of the animals treated with CsA were



Figs. 1–4. Light micrographs of haematoxylin-eosin stained pancreatic islets from mice. The animals had been treated for 5 consecutive days with 2 daily injections of saline + citric acid buffer (Fig. 1), cyclosporin A (50 mg/kg BW) + citric acid buffer (Fig. 2), saline + streptozotocin (40 mg/kg BW; Fig. 3) or cyclosporin A (50 mg/kg BW) + streptozotocin (40 mg/kg BW; Fig. 4). All micrographs were taken 14 days after starting the treatment. Note the normal appearance of the islets in Figs. 1 and 2 and the pronounced infiltration of mononuclear cells into the islets of the animals treated with multiple low dose injections of streptozotocin (Figs. 3 and 4). Magnification 384 ×

stained (50 mg/kg body weight) + SZ, compared with 52% in those animals treated with saline + SZ.

Normal histological appearance of the islets was found in the animals treated with saline, or CsA together with citric acid buffer, at all time points (Figs. 1 and 2). Occasionally, however, there was a widening of the intercellular spaces, suggestive of oedema, in the exocrine parenchyma in some of the animals exposed to the higher dose of CsA. The SZ-treated animals exhibited a variable islet morphology on day 7 with most animals showing an abnormal islet histology, in particular those simultaneously treated with CsA. On day 14 all SZ-injected animals had insulitis (Fig. 3 and 4) or showed only residual islets in the pancreatic sections. It is notable that CsA did not affect the degree of insulitis after the multiple SZ treatment (Table 4).

Discussion

This study confirms and extends previous observations suggesting that CsA treatment in conjunction with multiple low-dose injections of SZ in susceptible mice does not prevent the evolution of diabetes (Sestier et al. 1985; Kolb et al. 1985). Sestier et al. (1985) found that daily injections of CsA (50 mg/kg body weight) for 12 days potentiated SZ-induced diabetes and similar observations were made by Kolb et al. (1985) when CsA was given either at a dosage of 12 or 60 mg/kg body weight for 2–3 weeks. Since these failures to protect the mice

Table 4. Pancreatic islet histology rank in C57BL/Ks mice 3–14 days following intraperitoneal injections with streptozotocin (SZ; 40 mg/kg body-weight) or citric acid buffer (0.2 ml) for up to five consecutive days. Thirty min before the injections of SZ or citric acid buffer, the animals were given intraperitoneal injections of Cyclosporin A (CsA; 10 or 50 mg/kg body-weight) or saline (9 g/l; 0.2 ml)

Days after starting the treatment	Islet morphology rank											
Arbitrary class	Day 3				Day 7				Day 14			
	A	B	C	D	A	B	C	D	A	B	C	D
Saline + citric acid buffer	6	0	0	0	6	0	0	0	6	0	0	0
CsA (10 mg/kg body-weight) + citric acid buffer	6	0	0	0	6	0	0	0	7	0	0	0
CsA (50 mg/kg body-weight) + citric acid buffer	8	0	0	0	9	0	0	0	6	0	0	0
Saline + SZ	4	1	0	1	2	1	1	1	0	0	4	3
CsA (10 mg/kg body-weight) + SZ	7	0	0	0	1	1	2	3	0	0	6	0
CsA (50 mg/kg body-weight) + SZ	8	0	0	0	1	1	2	3	0	0	5	0

The islet morphology of each animal was ranked according to four arbitrary classes. *A* Normal islet structure; *B* Some mononuclear cell infiltration in the periinsular area; *C* Mononuclear cell infiltration in a majority of islets, i.e. insulitis; *D* Only a few residual islets displaying cellular disarray and pyknotic nuclei. The number of animals ranked into each class for the different experimental groups of mice are given

against multiple low-dose SZ induced hyperglycaemia could be due to the CsA doses used and the length of of CsA therapy, we therefore choose to administer CsA for only five days and at two doses, 10 and 50 mg/kg body weight in the present study. The former dose has been demonstrated to prevent the development of spontaneous diabetes in BB rats (Laupacis et al. 1983). These alterations in the CsA treatment did not counteract the SZ-induced hyperglycaemia in the C57BL/Ks mice, however, but rather enhanced the hyperglycaemic effect of the multiple SZ-injections.

A number of studies in rodents have suggested that higher doses of CsA in vivo may exert a directly harmfull effect on the pancreatic B-cells (Sestier et al. 1985; Kolb et al. 1985; Helmchen et al. 1984; Hahn et al. 1986) and it is likely that such an effect may be additive to a direct cytotoxic effect of SZ in the multiple-SZ model (Bonnevie-Nielsen et al. 1981; Sandler 1984). Although immune mechanisms probably contribute to the hyperglycaemia in this animal model of type I diabetes and this influence might be inhibited by CsA, the direct B-cytotoxic action of CsA (Andersson et al. 1984) may predominate and subsequently cause a potentiation of the hyperglycemia or a failing protection against hyperglycaemia. The present finding of a decreased number of labelled islets 3 days after starting the treatment, but an increase after 7 days may be interpreted to reflect an initial immunomodulation and amelioration of the SZ-diabetes followed by a cytotoxic effect in the B-cells.

The control animals given CsA and citric acid injections showed increased vascular permeability in the islets following Monastral Blue B injections which was very pronounced after 7 days in the mice given the high dose of CsA, whereas after 14 days no increased vascular leakage occurred in the islets. This effect was accompanied by a decreased number of visible islets using the frezee-thawing technique (Jansson and Hellerström 1981) on day 7 but normal values on day 14. It can be speculated that the five consecutive injections of CsA impaired the islet function transiently leading to an islet B-cell degranulation, making the islet cells non-distinguishable from the exocrine parenchyma in the frozen-thawed pancreatic preparations. Since the CsA effects were reversible it appears that an influence of shorter duration on the islet B-cells may not necessarily lead to a B-cytotoxic damage. It cannot, however, be excluded that the increased capillary leakage induced by CsA contributed to the potentiation of the hyperglycaemia, because this would allow an increased permeation of inflammatory cells into the islets and a subsequent release of inflammatory mediator substances. In this context the cytokine interleukin-1 has recently been suggested to exert a cytotoxic effect on pancreatic B-cells which can also be of relevance for the pathogenesis of type 1 diabetes (Mandrup-Poulsen et al. 1985; Mandrup-Poulsen et al. 1986; Bendtzen et al. 1986).

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