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Reperfusion injury of pancreas allografts: relation to islet cell function

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It is unknown to what extent preservation and/or reperfusion may damage islet cells in pancreas allografts. In this study, the release of insulin after reperfusion was used as a marker of injury to the islet cell and compared with the best insulin secretory response (ISR) after glucagon stimulation over a period of 100 days after pancreas transplantation.

Key words: Pancreas reperfusion injury – Pancreas transplantation

Patients and methods

All recipients suffered from diabetes mellitus type I, with absent C-peptide response after glucagon stimulation, and were treated with insulin 3–4 times daily; the pre-transplant hemoglobin (HbA_{1c}) level was 9.2 ± 4.1; average diabetes duration was 12 years; mean age was 36.5 years. The recipients' characteristics are summarized in Table 1. The technique of pancreas allograft transplantation is described in [1]. Briefly, a segment of duodenum and the pancreas are transplanted with bladder deviation. In the procedure with a pancreas transplantation alone, the spleen is included after irradiation ex vivo with 600 rad. All organs are preserved with UW solution. Immunosuppression consisted of cyclosporin A (CyA) 4 mg/kg IV, dosage adjusted after an initial oral dose with trough levels 0.1–0.2 mg/l (high performance liquid chromatography, HPLC, whole blood); PRN 60 mg on day 1, tapered to 10 mg on day 3, ultimately to 5 mg; azido thymidine (AZT) 1.5 mg/kg. The first anti-rejection treatment involved rATG, the second OKT3, the third PRN 100 mg 3 alternate days. Glucagon stimulation was carried out on day 1 after transplantation, then twice a week or more frequently depending on the clinical course. Glucagon 1 mg was given slowly (over 1 min) IV, and samples were drawn 5, 10, 15, and 30 min after injection. The ISR to glucagon was expressed as the incremental area under the curve (iAUC in mU/l per 30 min). The insulin release after reperfusion was measured directly before and every 15 min during the first 2.5 h after reperfusion of the implanted pancreas allograft. The iAUC was calculated and the release after reperfusion expressed as iAUC in mU/l per 150 min.

The insulin level was determined with a commercially available radioimmunoassay (RIA) (Pharmacia, Uppsala, Sweden) after polyethylene glycol (PEG) precipitation. The C-peptide content was determined with a RIA (Byk-Sangtec, Dietzenbach, FRG). The amylase activity was measured by catalyzing the hydrolysis of *p*-nitrophenyl-*a*-d-maltahexaoside at 37 °C for 3 min; a bichromatic rate technique (405 and 510 nm) was used to measure the absorbance of the developed *p*-nitrophenol.

Results and discussion

Table 1 summarizes the recipients' characteristics. No relation was found between either the cold or the warm ischemia time and the release of insulin after reperfusion. Table 2 shows the results of the ISR after glucagon stimulation. The correlation between the ISR and amylase excretion rate (AER; U/h) is also shown. There was no relation between amylase release after reperfusion and the highest AER after pancreas transplantation (data not shown). However, there was an inverse relation between insulin release after reperfusion (U/l per 150 min) and the maximum insulin secretion response after glucagon stimulation (U/l per 30 min) measured within the first

Table 1. Summary of recipient characteristics

Recipient			Pancreas transplant type	Follow-up (months)	Dr-mismatches	CIT (h)	Rejection episodes
No.	Sex	Age (years)					
1	M	36	PA	3	2	20	1
2	F	29	PA	6	2	13	3
3	M	32	SPK	18	1	12	1
4	M	36	SPK	6	1	19	1
5	M	48	SPK	12	2	11	0
6	F	23	PA	4	1	11	2
7	M	45	PAK	4	0	20	0
8	M	43	SPK	3	1	19	?

PA, pancreas-alone; PAK, pancreas after kidney transplant; SPK, simultaneous pancreas kidney transplant; CIT, cold ischemia time

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Table 2. Quantitative results of insulin secretory response (ISR) after glucagon 1 mg IV in pancreas allograft recipients (mU/l per 30 min); correlation with amylase excretion rate (AER)

Recipient	First ISR	Maximum pre-rejection		During rejection		Maximum post-rejection		Correlation with AER			
		Day	ISR	Day	ISR	Day	ISR	*n*	*r*	SEE	*P*
1	351	9	948	14	434	16	858	9	0.57	3677	0.11
2	323	11	3338	13	2434	20	5037	7	0.91	549	0.004
3	219	6	820	13	58	21	501	7	0.48	3618	0.27
4	125	4	177	7	114	14	800	5	0.55	4030	0.33
5[a]	347	–	–	–	–	–	1370	11	0.92	1313	0.0001
6	905	6	1561	14	141	48	561	9	0.91	1229	0.001
7[a]	493	–	–	–	–	–	1980	9	0.15	8087	0.68
8[a]	85	–	–	–	–	–	111	11	0.37	167	0.26

[a] No rejection in recipients 5 and 7; all responses of recipient 8 were low
SEE, standard error of estimate

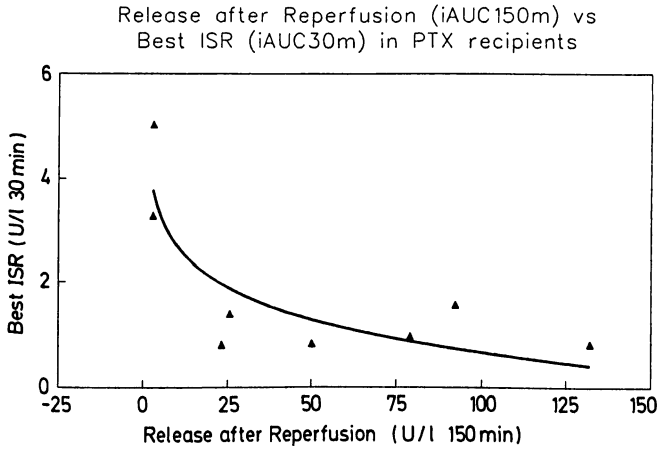

Fig. 1. Release of insulin after reperfusion vs maximum ISR after glucagon stimulation in pancreas transplant recipients

3 months after transplantation (Fig. 1). This relation was significant at the level of $P < 0.01$.

In conclusion, pancreas allografts varied considerably in their output of insulin directly after reperfusion. Furthermore, an inverse relation was shown between insulin release after reperfusion and stimulation, and no relation between amylase release after reperfusion and unstimulated maximum amylase secretion within 100 days after pancreas allograft transplantation.

Reference

1. Kootstra G, Van Hooff JP, Jorning PJG, et al (1987) A new variant for whole pancreas grafting. Early experience. Transplant Proc 19: 2314