MRI of acute rejection of transplanted pancreatic islets

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Introduction

Type-1 diabetes mellitus could be treated by pancreatic islets (PI) transplantation in some patients (1). Transplanted PI containing beta cells labeled by a superparamagnetic contrast agent can be easily visualized by MRI in vivo, since they appear as hypointense spots in the liver on T2*W MR images (2). The aim of this study was to investigate changes in labeled PI imaging during acute rejection in a rat animal model. We hypothesized that hypointense spots wane on MRI due to the destruction of labeled allogeneic PI in the course of rejection.

Subjects and Methods

PI were isolated according to a standard protocol (3) from Wistar and Lewis male rats. The isolated pancreatic islets were stained in CMRL-1066 medium (37°C, 5% atm. CO_2; Sigma) supplemented with the liver-specific magnetic resonance contrast agent Resovist® (0.5mmol Fe/ml, Schering) for two days (concentration of Resovist®: 5 µl /ml of medium). After removal from tissue culture, 2000 PI (Wistar PI n=10, Lewis PI n=6) were washed three times then slowly injected into the liver of Lewis rats with streptozocine diabetes (i.v., 50mg/kg). Blood glucose levels were measured every other day.

The anesthetized animals were scanned by a 4.7 T Bruker Biospec spectrometer equipped with a resonator coil. We used a gradient echo sequence, TR = 80ms, TE = 3.4 ms, slice thickness = 2 mm, slice separation = 3 mm, number of slices = 8, number of averaging = 16, FOV = 6 cm and matrix = 256x256.

Rats with syngeneic PI were scanned weekly for 24 weeks after transplantation and recipients treated by allogeneic PI were scanned weekly for 50 days.

The presence of iron oxide nanoparticles inside the cells of the pancreatic islets was confirmed by Prussian blue staining.

Results

Histology confirmed the rejection of allogeneic islets in all cases. Staining with Prusian blue showed the presence of iron-oxide nanoparticles inside the cells of PI (Figure 1). Normal glycaemia was established in 3 days after transplantation in all recipients. In contrast to syngeneic PI, the function of allografts failed in 11 days (Figure 2). The syngeneic PI were clearly visualized within the liver during the entire measurement period as hypointense spots (size 0.1-3mm^2) on T2*W MR images (Figure 3a,b). The failure of allogeneic islets was followed by the disappearance of the hypointense spots (Figure 3c,d) and the total destruction of PI structure as confirmed by histology.

Discussion and Conclusions

Our results demonstrate that the MR technique easily follows the fate of transplanted pancreatic islets labeled by a superparamagnetic contrast agent. Using this method we can monitor in vivo the acute rejection of transplanted pancreatic islets on MR images. The hypointense spots were significantly reduced only in rats with allogeneic islets, and histology confirmed the destruction of the transplanted islets. Thus, this method of monitoring the acute rejection of pancreatic islets in an animal model represents a promising step towards possible clinical application in human medicine.

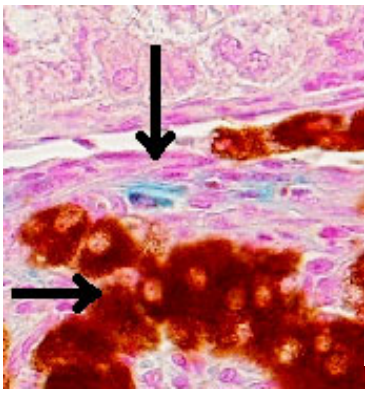

Figure 1: Syngeneic pancreatic islets. Double-staining for Prussian blue and insulin confirmed the presence of iron nanoparticles (vertical arrow, blue) and insulin (horizontal arrow, brown).

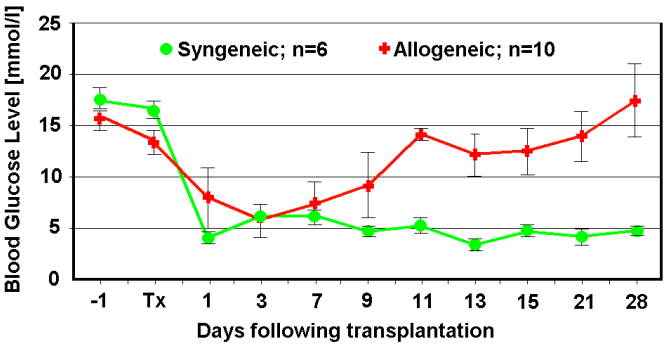

Figure 2: Blood glucose levels of diabetic rats. Blood glucose levels were normalized in all animals by 3 days following transplantation and remained normal throughout in the group of syngeneic rats. The islets were rejected on average at 10,4±1,2 days after transplantation in the group of allogeneic rats.

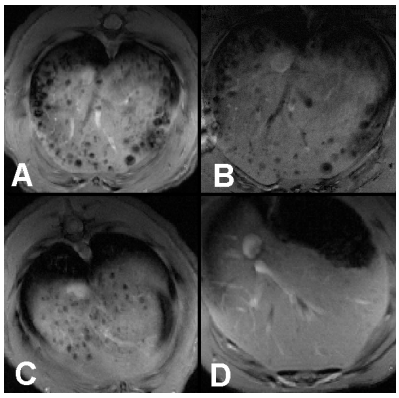

Figure 3: MRI in vivo of a rat liver imaged one (A, C) and seven (B, D) weeks after transplantation of labeled syngeneic (A, B) and allogeneic (C, D) pancreatic islets (hypointense spots).

References

1. Efrat S. Cell replacement therapy for type 1 diabetes. *Trends Mol Med*. 2002 Jul;8(7):334-39.
2. Jirák D, Kříž J, Herynek V, Andersson B, Girman P, Saudek F, Hájek M. MRI of transplanted pancreatic islets. Mag Reson Med; in press.
3. Lacy PE, Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes*. 1967 Jan;16(1):35-9
4. Jirak D., Kriz J., Herynek V., Andersson B., Girman P., Burian M., Saudek F., Hajek M. MRI of transplanted pancreatic islets. A preliminary in vitro study. *Magma*. 2003 Sep; 16(7):S340.

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