

MRI of transplanted pancreatic islets

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Introduction

Type-1 diabetes mellitus is characterized by the autoimmune destruction of insulin-producing pancreatic beta-cells, which causes metabolic disturbances, manifested mainly by high levels of blood glucose. One of the promising treatment methods is the transplantation of pancreatic islets containing beta-cells (1). Autologous pancreatic islets were successfully visualized using MR imaging of labeled lymphocytes in an autoimmune model (2). The aim of this study was to develop a MR technique, which could be used for monitoring of the distribution and further fate of transplanted pancreatic islets in vivo in an animal model.

Subjects and Methods

Pancreatic islets were isolated according to standard protocol (3). The isolated pancreatic islets were stained in the medium CMRL-1066 (37°C, 5% atm. CO₂; Sigma) with the liver-specific magnetic resonance contrast agent Resovist® (0.5mmol Fe/ml, Schering) for two days, using a contrast agent concentration of 50 µl per 10ml of the medium. 2500 purified and labeled islets were transplanted into the liver through the portal vein. The portal vein was ligated 5 minutes after transplantation. Transplantation was performed on 5 healthy Lewis rats and 5 Lewis rats with induced diabetes type-1 (conditioned by streptozotocin).

The animals were scanned by a 4.7 T Bruker Biospec spectrometer equipped with a home-made surface 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.

Two diabetic rats were scanned once three weeks after transplantation, while three diabetic rats were scanned weekly for 50 days following transplantation. The transplanted healthy rats were scanned weekly for 20 weeks after transplantation to verify the long-term viability of the islets.

The presence of iron oxide nanoparticles inside the cells of the pancreatic islets was confirmed by transmission electron microscopy. Islets were dehydrated, immersed into propylenoxide and embedded in resin Agar 100 (Agar Scientific Ltd, Standsted, England). 50 nm ultra thin sections were stained using Reynold's lead citrate and subsequently examined in a transmission electron microscope (Philips Morgagni 268). The iron content in the isolated pancreatic islets was determined after mineralization by spectrophotometry (Spectroflame M120S, Spectro inc., Littleton, MA, USA).

Results

Transmission electron microscopy confirmed the presence of iron-oxide nanoparticles inside the cells of the pancreatic islets. Nanoparticles were found in different cell structures (Figure 1). The mean concentration of iron was 270 ng per one islet. The labeled pancreatic islets were clearly visualized in the liver during the entire measurement period in all diabetic and healthy rats as hypointense spots (size 0.1-3mm²) on the MR images (Figure 2). The pancreatic islets were distributed within the whole liver.

We observed a significant decrease in blood glucose levels in diabetic rats; normal glycaemia was reached by 1 week after transplantation (Table1). The labeled islet isographs survived in the diabetic rats until the end of the experiment on the 50th day post-transplantation.

Discussion and Conclusions

Our results demonstrate that labeled pancreatic islets can be easily visualized by MR in vivo. The islets labeled by a superparamagnetic contrast agent exhibit themselves as hypointense spots in the liver on T2*W MR images. Our study shows that transplanted islets are functional, although our previous study demonstrated a slightly decreased in vitro insulin production in Resovist® treated pancreatic islets (4). The contrast agent employed is clinically approved as a liver-specific blood pool agent for human use and does not require any facilitation of iron uptake or modification of the pancreatic islets. Thus this study represents a promising step towards possible clinical application in human medicine.

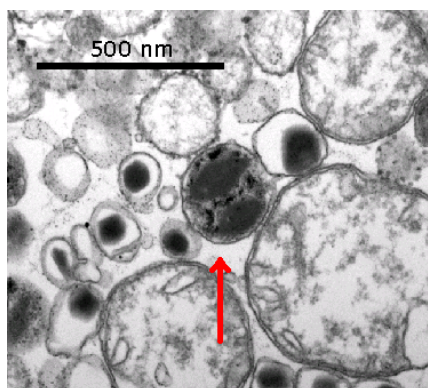


Figure 1: Electron microscopy of isolated labeled pancreatic islets. Arrow points to a lysosome containing the nanoparticles.

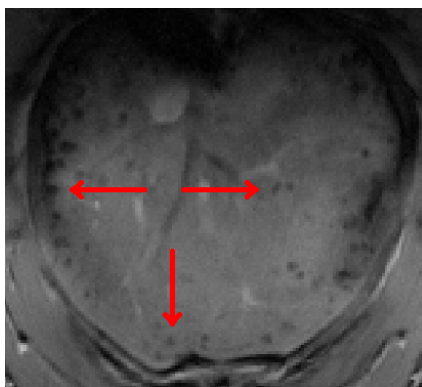


Figure 2: MRI in vivo of a rat liver imaged 20 weeks after transplantation of labeled pancreatic islets (arrows point to islets as an example).

Before TX [mmol/l]	3 days after TX [mmol/l]	14 days after TX [mmol/l]
22.0 ±6.0	9.0 ±3.7	5.4 ±0.7

Table 1: Blood glucose levels of diabetic rats. Two weeks after transplantation of pancreatic islets, the diabetic rats had normal blood glucose levels.

References

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