Manganese enhanced MRI detects pancreatic beta cell function *in vivo*

P. F. Antkowiak[1], S. A. Tersey[2], R. G. Mirmira[2,3], and F. H. Epstein[4,5]

[1]Biomedical Engineering, University of Virginia, Charlottesville, Virginia, United States, [2]Medicine, University of Virginia, [3]Pharmacology, University of Virginia, [4]Radiology, University of Virginia, [5]Biomedical Engineering, University of Virginia

Introduction

Type 1 diabetes is a metabolic disorder characterized by an inability to maintain normoglycemia due to an inflammatory process that selectively destroys the insulin-producing β-cells of the pancreas. In healthy individuals, pancreatic β-cells release insulin into the bloodstream in response to a sensed elevation in blood glucose. Insulin production is initially stimulated by the transport of glucose from the bloodstream into the β-cell and is immediately preceded by a flow of extracellular calcium (Ca^{2+}) ions into the β-cell through voltage gated Ca^{2+} channels. Manganese (Mn^{2+}) is a paramagnetic T1 relaxation agent capable of entering β-cells through Ca^{2+} channels, and manganese enhanced MRI has been shown by Gimi et al. to be an effective means for probing β-cell function *in vitro* (1). We performed an initial study *in vivo* using manganese enhanced MRI to measure β-cell function either with or without glucose stimulation in normal mice and in a Type 1 diabetes mouse model.

Methods

After >2 hours of fasting, six-to-eight month old normal and diabetic C57BL/6J mice underwent MR imaging on a 7.0T Clinscan system (Bruker, Etlingen, Germany). All animals received a bolus of either 100μl saline (n = 5 normal, n = 4 diabetic) or 1.5 mg/g glucose (n = 5 normal and diabetic) intravenously via indwelling tail vein catheter 2 minutes prior to an intraperitoneal injection of 50 μl Mn^{2+} (0.1 μmol/g). Images of the abdomen were acquired serially at 3 minute intervals immediately after Mn^{2+} injection until 45 minutes post-injection using an inversion recovery sequence with a segmented GRE readout. Specific MR parameters were TR = 3000 ms, TI = 580 ms, TE = 3.05 ms, slice thickness = 0.5 mm, imaging flip angle = 20°, FOV = 35 mm, matrix = 192 x 153, BW = 260 Hz/pixel, number of segments = 9, and number of averages = 3. Type 1 diabetes was induced by a single intraperitoneal injection of 180 mg/kg streptozotocin (STZ), a drug that is selectively toxic to pancreatic β-cells, and mice were confirmed to be diabetic by having 3 consecutive blood glucose readings from cut tail tips above 250 mg/dl. After both glucose and saline imaging experiments were completed for each mouse, animals were sacrificed and their pancreata were harvested for measurement of insulin content via mouse insulin ELISA. Time-intensity curves (TICs) were generated by drawing regions of interest in the pancreas, liver, and in the background using Mean Curve (Siemens Medical Solutions). Curves were fit to a scaled sigmoid function and statistical analysis was performed on the sigmoid function plateau height using two-way ANOVA.

Results

Figure 1 shows the results from a typical imaging experiment. TICs from the pancreas were baseline-subtracted and normalized to peak values of liver TICs to account for variations in the delivery of Mn^{2+} to the pancreas due to factors such as cardiac output. Normalized pancreas signal is plotted vs. time for normal mice (Fig 2a) and diabetic mice (Fig 2b). Sigmoid function plateau height was 51% greater after glucose injection compared to saline injection in normal mice ($p < .01$); this difference was not observable in diabetic mice (p = ns). Pancreatic insulin content was 942 pmol/mg pancreas in normal mice and 41 pmol/mg pancreas in diabetic mice (p = ns).

Discussion

We present what we believe to be the first study using Mn^{2+} enhanced MRI to measure murine β-cell function *in vivo*. In normal mice, a significant increase in normalized pancreas signal intensity was seen after glucose injection, likely due to an increase in Mn^{2+} entry through glucose-stimulated Ca^{2+} channels. In STZ-induced diabetic mice, normalized pancreas signal did not increase after glucose injection since most pancreatic β-cells were destroyed as verified by insulin content assays. This study indicates that Mn^{2+} enhanced MRI has potential for noninvasively evaluating β-cell function in future longitudinal studies evaluating potential therapies and measuring the effectiveness of islet transplants.

References

1). Gimi, B. et al. *Cell Transplant*. 2006; 15 (2): 195-203

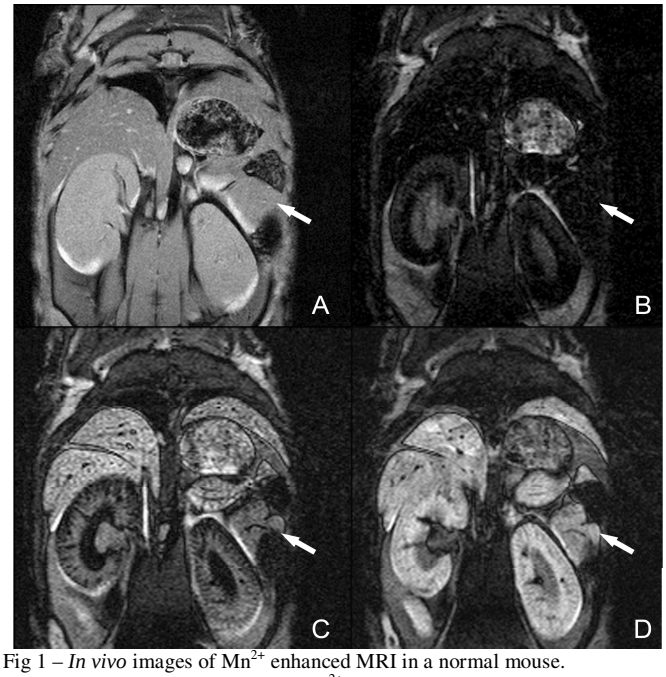

Fig 1 – *In vivo* images of Mn^{2+} enhanced MRI in a normal mouse. a). Anatomical reference. b). Pre-Mn^{2+} IR image with pancreas nulled. c) and d). IR images taken at 5 and 45 minutes post Mn^{2+} injection. *White arrows* denote pancreas.

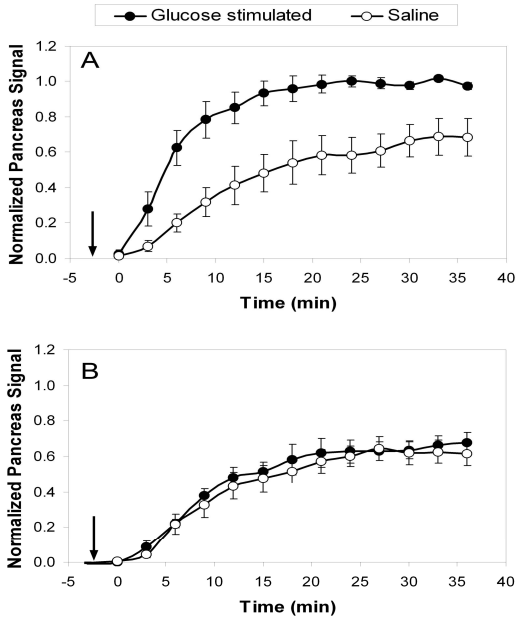

Fig 2 – TICs of normalized pancreas with or without glucose a). Normal mice (n= 5 saline and glucose). b). Diabetic mice (n= 4 saline, n = 5 glucose). *Black arrow* indicates time of saline/glucose injection. Mn^{2+} was injected at t = 0.