Manganese Enhanced Magnetic Resonance Imaging (MEMRI) of Endogenous Rodent Pancreas Activation

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Introduction:

Diabetes is a metabolic disorder cause by inadequate supply or utilization of insulin, secreted by pancreatic beta cells. Presently pancreatic ß-cell function is assessed via insulin release or indirectly via serum glucose levels. The lack of understanding about pancreatic physiology and ß-cell mass is a major hurdle in therapy development. Knowing the functional efficiency of the pancreas would certainly be beneficial in the development of novel therapies aimed at maintaining or increasing ß-cell function. Thus, development of non-invasive imaging modalities to evaluate ß-cell function is needed.

ß-cells are stimulated as a result of increased blood glucose levels which results in calcium (Ca^{+2}) uptake through voltage-gated channels followed by insulin release. Manganese ions (Mn^{+2}) are a Ca^{+2} analog and a T1 relaxation agent. Therefore ß-cells activated by increased glucose in the presence of Mn^{+2} will demonstrate a change in MR signal intensity compared to non-activated cells. Here we present *in-vivo* functional imaging of rodent pancreas via Mn enhanced MRI (MEMRI) in response to glucose stimulation. Anatomically it is difficult to image the whole mouse pancreas, due to its low density and its location as it originates near the duodenum and spreads through different imaging planes. Peristaltic motion and a limitation on the number of slices per breath cycle further restrict the image acquisition. To overcome these constraints, a segmented Magnetization Prepared RApid Gradient Echo (MP-RAGE) imaging pulse sequence was applied to achieve significant T1 weighted contrast in response to glucose stimulation. The results demonstrate a significant change in image contrast due to the metabolic effects of glucose in the pancreatic regions.

Method and Material:

Male C57 Black mice weighing 20-30 g (Harlan Sprague Dawley, Inc., Indianapolis, IN), were housed in the University of Chicago's animal facility. All surgical procedures were performed in accordance with University Animal Care Guidelines. Animals were ventilated with 1.5-2% isoflurane and the tail vein was catheterized for $MnCl_2$ and glucose infusion. Vital signs were monitored via ECG, respiratory pad, and rectal thermometer using SA Instrument (Stony Brook, NY) software. Imaging was performed on a 9.4T horizontal bore Bruker (Billerica, MA) magnet with homebuilt transmit-receive birdcage resonator. Control, post contrast and post glucose, T1-weighted images were obtained using MP-RAGE (FOV = 2.9 x 2.9 cm, matrix size = 128 x 128, echo time = 3.63ms, segment repetition time = 2.0 sec, inversion delay = 1000 ms, 4 segments, segment duration = 347 ms. NEX =6). $MnCl_2$ (3mM) was infused at 20 µl/min for 4 min giving a final dose of 10.0 nmol/g BW and IV bolus glucose injection was administered (1g/kg).

Results and Discussion:

Figure 1b is the corresponding MR image of Figure 1a in which part of the activated pancreas with some pockets of hyper intense regions are visible. Figure 2 show endogenous pancreas activation at different imaging time intervals (a) control, (b) post Mn, and (c) post glucose. Post Mn images show a leaf like pattern which is broken to pockets of activation following glucose. A signal enhancement of 70% and 61% was reported following Mn and glucose activation respectively compared to the control. .

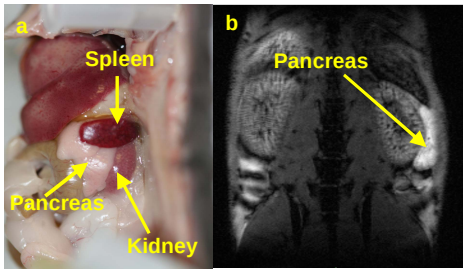

Figure 1(a) side view of mouse pancreas connected to the spleen and resting on the kidney. (b) Corresponding MR image of mouse pancreas with hyper intense regions of activation.

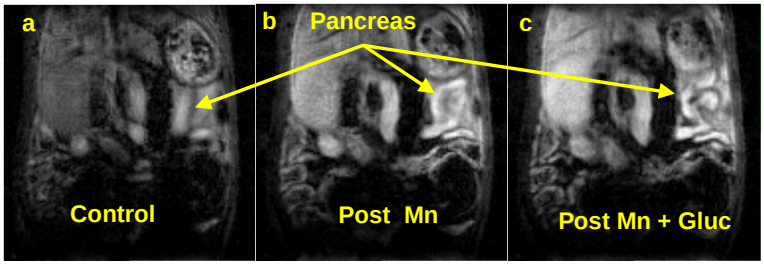

Figure 2. Coronal view of mouse abdominal cavity as arrow indicating the part of the pancreatic regions. (a) Control (b) Post Mn, (c) Post Mn plus Glucose, illustrating the dynamic impact of glucose on image contrast.

Conclusion:

In-vivo functional imaging of endogenous pancreas is possible despite complications of morphology and motion. Multishot MPAGE provided enhanced T1 weighting, which led to increased sensitivity to Mn. Here we demonstrated the dynamic impact of manganese and the glucose on image contrast in the pancreas. These data suggest that this technique may be useful in *in vivo* studies of progressive ß-cell dysfunction associated with diabetes.