Imaging pancreatic islets ex vivo by ultra high field of 14T, combining manganese and iron-oxide enhanced MRI

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Purpose

In Type 1 and Type 2 diabetes the gradual loss of pancreatic β–cell function and mass leads to impaired regulation of blood glucose levels due to insufficient insulin secretion. Monitoring of pancreatic β–cell status would enable the estimation of the stage of pathology. β–cells are located in the endocrine part of pancreas, in the islets of Langerhans which, in the adult, make up 1% of the total pancreas tissue, have diameter of 30-600μm, and are distributed across the organ. Imaging these islets in vivo is challenging, and success in ex vivo imaging of intact organ is an important first step. We utilized for the first time ultra high field of 14.1T in combination of manganese- and iron-oxide nanoparticle-enhanced MRI to assess how MRI can image pancreatic structures ex vivo.

Materials and Methods

Eight mice and two rats were subjected either to i.v. $MnCl_2$ infusion together with i.p. glucose stimulus (glucose activates the islet β–cells, and promotes their Mn^{2+} uptake; 3 mice), iron-oxide nanoparticle injection into the pancreatic exocrine duct system (1 rat), a combination of these procedures (3 mice), or no preparation (2 mice, one rat, which served as controls) In all cases the pancreata were dissected, fixed in 4% PFA, and placed into perfluoro polyether for imaging after a 6h fixation. Ex vivo samples were then imaged in a 14.1T 26cm horizontal bore scanner using quadrature half-volume coil 20mm in diameter. High resolution images were acquired using gradient echo multi slice sequence with TR=282ms, TE=7ms, flip=60°, 30 averages 14 0.3mm-thick slices, FOV 26*25, data matrix 512*512 (51*49μm in plane resolution) to cover the whole mouse pancreas. Imaging took time only 1h 12min.

Results

Fine structure of mouse pancreas was unrevealed by the different combinations of contrast agents. Figure 1 summarizes the findings.

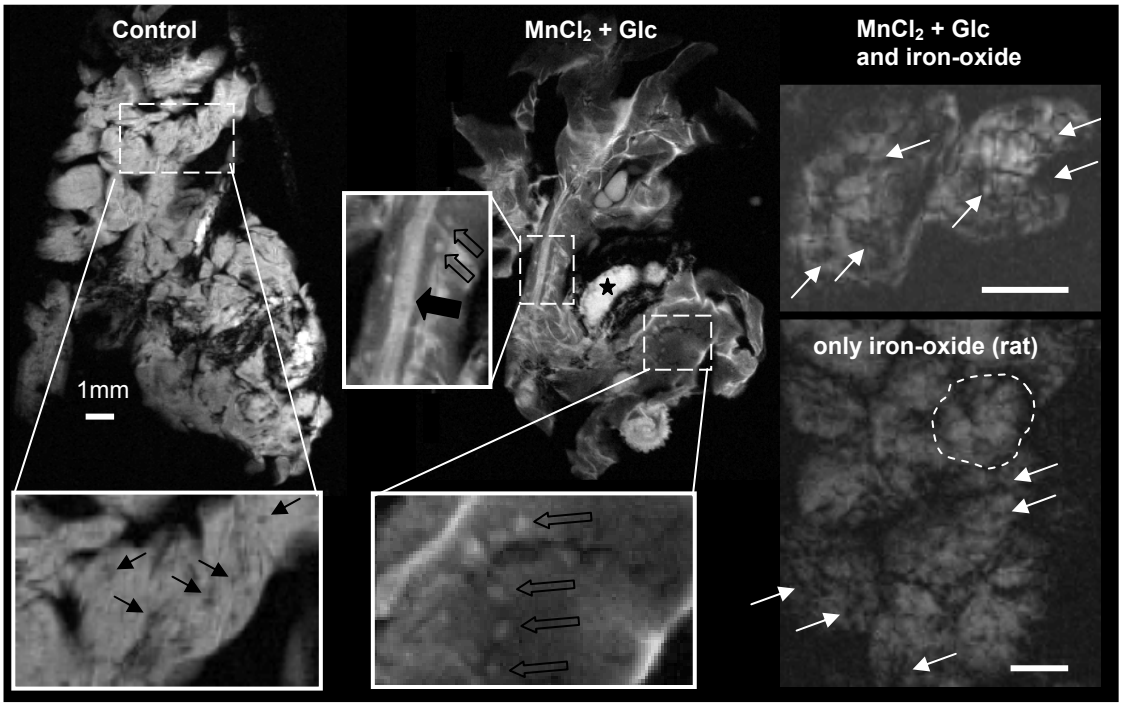

Figure 1. High resolution images of mouse pancreas. Scale bars equal 1mm. **Left:** In control mouse optimized contrast reveals lobar organization, dark acini dots (black arrows) and branching duct system. **Middle**: $MnCl_2$ and glucose administration enhanced tubular (black thick arrow) and round-ovoid structures (open arrows), presumably representing ducts and pancreatic islets. Ganglia is marked with a star. **In right** column, bottom (rat): iron-oxide (in ducts) reveals lobular structure of the gland (dotted circle) and dark ducts (white arrows). Same is true when combining $MnCl_2$ plus glucose and iron-oxide (right column, on top, mouse) in which case tissue in between the dark ducts shows signal increase.

Conclusions

High resolution MRI at 14T reveals all the main pancreatic structures, including lobules, branching duct tree with terminal acini. The manganese and glucose contrast, together with the infusion of iron oxide particles, also delineated structures which, by their position, shape and size are likely to correspond to individual pancreatic islets. Indeed, the lateral resolution achieved, about 50*50μm, is sufficient to visualize single islets, even in the absence of any direct labeling. However, the combination of the positive manganese contrast and of the negative iron-oxide contrast deteriorated the identification of islet-sized bright structures. Alone, manganese infusion enhanced the contrast of the main ducts, mm-scale lymphatic ganglia, and the mesh of the inter-lobular connective and adipose tissue. The precise identification of these structures was made possible by correlating the MRI images with histology. A definitive identification of the putative pancreatic islets by a similar approach is in process. These results pave the way towards similar in vivo approaches, where this same 50*50*300μm resolution and contrast can be achieved with ~1h scanning time.

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