Quantitative pancreatic β cell MRI using manganese-enhanced Look-Locker imaging and two-site water exchange analysis

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Introduction: Pancreatic β cells are responsible for synthesizing and releasing insulin into the blood stream and play a critical role in maintaining blood glucose homeostasis. In type 1 diabetes mellitus (T1DM), β cells are destroyed by an autoimmune process. Though β cells play a central role in both the progression of and potential therapies for diabetes, there is currently no established method for noninvasively assessing β cell mass and function during disease progression or the course of therapy. The purpose of the present study was to develop and evaluate quantitative β-cell MRI using manganese (Mn^{2+}) labeling of β cells, T1 mapping, and a two site water exchange model. Mn^{2+} ions, which are similar to Ca^{2+} ions in size and valence, enter β cells through voltage-gated Ca^{2+}channels (VGCCs) (Fig 1A), leading to a compartment-dependent Mn^{2+} concentration (higher inside β cells, lower in the extra-β-cell space). As Mn^{2+} ions increase the spin-lattice relaxation rate R1 of nearby water protons, Mn^{2+}-enhanced T1-weighted MRI after glucose infusion has previously been demonstrated to be sensitive to β cell mass. Building on this mechanism of Mn^{2+} labeling of β cells and these promising initial MRI results, we sought to explore whether a two-site exchange model (Fig 1B) of T1 relaxation would be well-suited for Mn^{2+}-enhanced MRI of the pancreas, and whether model parameters would quantitatively reflect the status of β cell mass and function.

Materials and methods: Normal, pharmacologically-treated, and diabetic mice underwent intravenous injection of glucose and intraperitoneal injection of $MnCl_2$. Look-Locker MRI was performed to measure T1 relaxation of the pancreas and two-site water exchange analysis was used to estimate model parameters including the intra-β-cell R1 and the intra-β-cell fraction. Normal mice were injected with 1.5 g/kg glucose (n = 6) or 100 μL saline (n = 6). For pharmacological treatment, normal mice were injected with the VGCC blocker nifedipine + glucose (n = 6, 10 mg/kg nifedipine + 1.5 g/kg glucose); the K_{ATP} blocker tolbutamide (n = 6, 10 mg/kg), which activates β cell VGCCs; or the K_{ATP} opener diazoxide + glucose (n = 6, 15 mg/kg diazoxide + 1.5 g/kg glucose), which closes β cell VGCCs. T1DM was induced with an injection of 180 mg/kg streptozotocin (STZ), which selectively destroys β cells, and n = 6 T1DM mice were injected with 1.5 g/kg glucose. Shortly after glucose and/or pharmacological injections, mice were injected with 0.1 μmol/kg $MnCl_2$ to label β cells. Look-Locker MRI was performed after $MnCl_2$ injection to measure T1 relaxation of the pancreas and two-site water exchange analysis was used to estimate model parameters including the intra-β-cell R1 and the intra-β-cell fraction, hypothesized to be indicators of β-cell function and mass, respectively.

Results: Data shown represent mean ± standard deviation. The time course of intra-β-cell R1 for glucose-injected normal mice is shown in Figure 2 (solid line). Nifedipine significantly reduced the intra-β-cell R1 compared to normals injected with glucose ($p < .05$). Tolbutamide caused a significant increase ($p < .05$) in intra-β-cell R1 relative to normal mice given saline (Fig. 3A), while diazoxide abolished the intra-β-cell R1 increase that occurs with to glucose stimulation (Fig 3B, $p < .05$). Intra-β-cell R1 was reduced in diabetic mice (Fig 2, dashed line) compared to normals at all measured times, with statistical significance at 1 and 2 hours. The intra-β-cell fraction was significantly higher in normal mice injected with glucose than in their diabetic counterparts (4.1 ± 0.1% vs. 2.6 ± 0.1%, $p < .001$).

Conclusion: We developed two-site exchange analysis of pancreatic T1 relaxation after injection of $MnCl_2$ and used it to probe model parameters that reflect β cell mass and function. Two site exchange analysis resolved the acquired MR signal into two compartments: one arising primarily from intra-β-cell water protons with a higher R1, and one arising from extra β-cell protons with a lower R1, and it provided for the calculation of the intra-β-cell R1 and the relative size of the intra-β-cell compartment. Results using pharmacological challenges support the hypothesis that these methods are sensitive to changes in beta cell function. Results in diabetic mice support the hypothesis that these methods are sensitive to changes in beta cell mass. These methods may be useful for monitoring disease progression and therapy in T1DM.

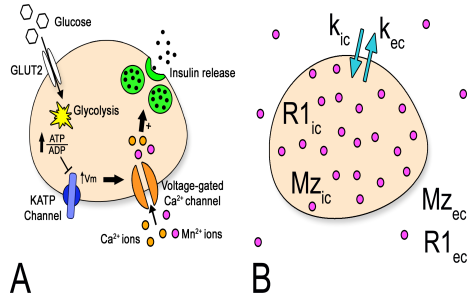

Figure 1 (above) – A). Insulin release schematic. B). Two compartment model of Mn^{2+}-enhanced pancreas.

Figure 2 (below): intra-β-cell R1 time course

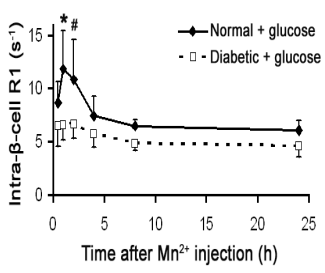

Figure 3 (right): intra-β-cell R1 comparison