Functional Imaging of Brown Fat in mouse

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Introduction: The brown adipose tissue (BAT) is a type of fat that modulates both basal and inducible energy expenditure in mammals. Its presence in adult humans has recently gained tremendous interest due to its implication in the development of obesity [1,2,3] and as a potential target for treatments [2]. Compared to white adipose tissue (WAT), BAT has numerous mitochondria and uncoupling protein 1 (UCP-1), and is highly metabolically active. However, despite their importance and implications in obesity, BAT detection is challenging due to the lack of specific marker in vivo. Most imaging of BAT has been done by radioactive fluorodeoxyglucose (FDG) PET, which is limited by its low resolution and radioactivity. Recently BOLD and blood volume-based fMRI was proposed for imaging active BAT [4,5], though their susceptibility-based contrast may suffer from artifacts in body imaging. Previously, we proposed Manganese Enhanced MRI (MEMRI) to map active BAT in the mouse in vivo [6]. Here we evaluated whether MEMRI enters BAT through Ca2+ channel or perfusion.

Methods: All animal experiments were approved by the local Institutional Animal Care and Use Committee (BMSI, ASTAR, Singapore). C57BL/6 (21 ± 0.1 g, 8-12 weeks) female mice were used in this study. Anesthesia was induced by 2% isoflurane and then maintained at 0.5-1.5 % throughout the imaging session in 100% O_2 via a nose cone. Body temperature was measured via a rectal probe and maintained with a MRI-compatible feedback heating system throughout the whole experiment at either 36 ± 0.1 °C for the control group or at 28 ± 0.2 °C for the cold exposure group. MRI were acquired using a 9.4T (Agilent, USA) scanner with a quadrature volume coil for RF transmission and a single-loop surface coil (1.5 cm in diameter) for receiving. The coil was carefully positioned above the interscapular BAT depot. Dynamic T_1-weighted MRI was acquired using 3D-MPRAGE (TR 8 ms, TE 2.5 ms, 1 mm slice thickness, 128x128x32 matrix, FOV 3.0x3.0 cm) for 2 hr. After 20 min of baseline acquisition, 5.93mg/kg/h of $MnCl_2$ was continuously infused i.v. for 60 min. Mean signal intensity was then extracted from ROIs drawn in the BAT, WAT, and muscle (MUS) tissue.

Results: High uptake of Mn^{2+} is observed in the subcutaneous fat in the interscapular area under cold exposure (fig. 1a). A Calcium blocker 10mg/kg, was injected before Mn^{2+} under cold exposure, which abolished uptake of Mn^{2+} (Fig. 1a). To determine whether the uptake was related to perfusion, a bolus of Gd-DTPA (1mg/kg). Indeed compared to warm exposure where Gd uptake in the BAT was negligible but significantly increased under cold exposure (Fig. 1b, 1c). This shows that BAT activated under cold exposure increases perfusion as well.

Discussion and Conclusion: We demonstrated MEMRI as a functional imaging method to detect brown fat activation in the mouse. Taken advantage of the increased Ca^{2+} flux in BAT by adrenergic activation, Mn^{2+}, as a Ca^{2+} analog, provides a sensitive way to detect functional activation at high resolution. An insignificant uptake of Mn^{2+} seen in mice maintained at normal temperature suggests the induced Mn^{2+} uptake following cold exposure. Gd contrast may be another way to detect increased perfusion in BAT, but the MUS perfusion also increased and the dosage is 10x higher than clinical dose. Together with other anatomical imaging of fat, MRI could be a powerful tool to study BAT in animal models of metabolic diseases.

References: [1] Nedergaard et al, Cell Metab 11(4) 2010; [2] Nedergaard et al, Am J Physiol Endocrinol Metab 293(2) 2007; [3] Nedergaard et al, Ann N Y Acad Sci. 2010; [4] Khanna et al, MRM 68(4) 2012; [5] Chen et al, Obesity 20(7) 2012; [6] Lee et al, Am J Physiol 264(1 Pt1) 1993.
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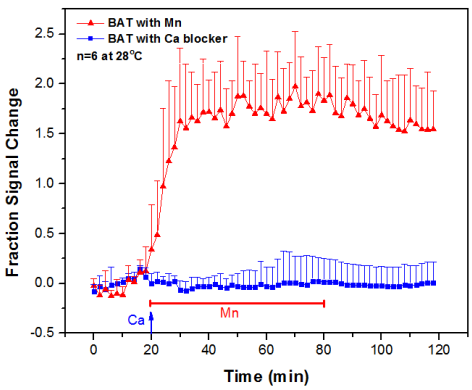
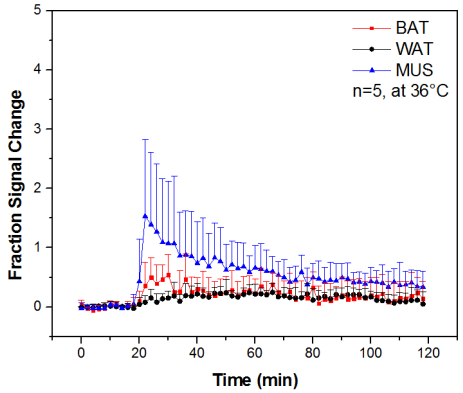


(a)



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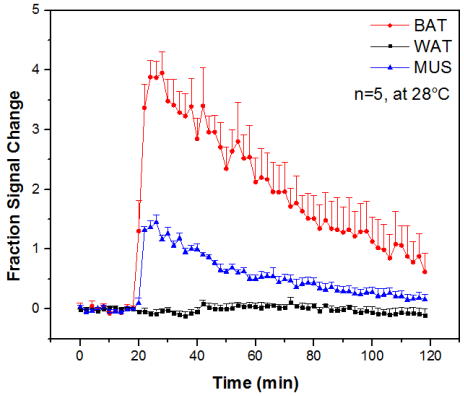

(c)