

## Detection of brown fat mass and activity by hyperpolarized xenon MR

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**Introduction:** Brown adipose tissue is a tissue specialized for non-shivering thermogenesis. It has recently become the focus of much research attention due to its implication in the development of human obesity[1,2]. Despite its importance, the detection of this tissue by conventional imaging methods presents several challenges. <sup>18</sup>FDG-PET fails to reliably detect the metabolism of this tissue since the main substrates for BAT thermogenesis are fatty acids, not glucose[2]. MRI, on the other hand, detects tissue fat fraction [3], which is known to depend on subject adiposity and have a large inter- and intra- subject variability. Here we investigate the use of HP xenon MR for the detection of BAT activity and compare this methodology to <sup>18</sup>FDG-PET and proton MRI in both lean and obese animals.

**Methods:** Both rats (8-female Fisher rats at 6 weeks of age), and mice (10 C57 female and 15 ob/ob female) were used for these studies. All MR studies were conducted on a 9.4 T small animal Bruker system using a surface xenon coil, accurately located above the inter-scapular brown fat tissue, and positioned inside an external volume proton coil, used to collect spin echo images and localized spectra for reference and water/fat quantification in BAT. For all xenon scans the animals were anesthetized with Nembutal, intubated and mechanically ventilated with a mixture of oxygen and natural abundance (26% <sup>129</sup>Xe) xenon, hyperpolarized up to 9.5% by SEOP using a commercial polarizer (Polarean, Inc, Research Triangle Park, NC). Dynamic imaging (Gradient Echo, FOV=5.5cm, TR=4s, NA=2, TE=2.5ms, MTX=64X32) and spectroscopy data (90 degree flip angle adiabatic excitation pulse, TR=4s, NA=15) were acquired before and during stimulation of BAT, the latter achieved by an injection of norepinephrine (2mg/kg). <sup>18</sup>FDG-PET/CT scans were conducted on the same animal or on a littermate, using a GE eXplore Vista small animal system. <sup>18</sup>FDG was injected right after the injection of NE or saline, to perform time-uptake analysis and indirectly evaluate tissue blood flow. At the end of the studies histology was used to determine tissue fat content (H&E staining) and thermogenic capacity (UCP1-staining).



Figure 1 Map of the dissolved phase signal acquired in an obese mouse before and during stimulation of BAT activity. The large enhancement in the xenon signal dissolved into BAT (see ratio between the dissolved phase and the gas phase peak in the insets) allows a clear delineation of the interscapular BAT depot

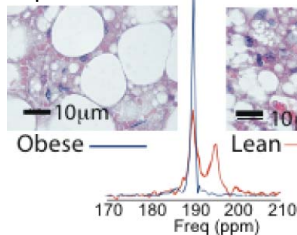


Figure 3: Xenon spectra acquired from lean and obese mice during stimulation of BAT show a large variation in the amount of xenon dissolved in fat versus that dissolved in tissue cytoplasm. Accounting for the different solubility of the gas in the two compartments, the ratio between these two peaks, seems to correlate well with mean tissue hydration.

Figure 1 Comparison between HP <sup>129</sup>Xe and <sup>18</sup>FDG-PET detection of brown adipose tissue in obese mice. Right, image of the dissolved phase HP xenon signal overlaid onto an anatomical spin echo 1H image in an obese mouse. Left <sup>18</sup>FDG-PET scan on a littermate. While HP Xenon produces a background free map of the interscapular BAT depot, the same tissue is hard to visualize in <sup>18</sup>FDG PET scan due to its reduced glucose uptake, comparable, on these animals, to that of nearby muscle.

**Results:** Our studies show that HP xenon can be used to detect BAT activity, during which a more than 100 fold enhancement can be observed in the xenon signal dissolved in BAT. Comparison between dynamic spectroscopy data and histology reveals also the possibility to detect average tissue hydration (i.e. water-fat content) as well as the possibility to detect brown fat thermogenic activity and fatty acid consumption in real time (data not shown). Compared to <sup>18</sup>FDG-PET and proton MRI this technique was able to detect active BAT (UCP1-positive) in obese animals that appear to have a reduced <sup>18</sup>FDG uptake, compared to that of nearby muscle, and a fat fraction similar to the nearby WAT (~80%).

**Conclusions:** Our work show that HP xenon is the ideal probe to detect BAT activity. The enhancement of the xenon signal dissolved in BAT during stimulation and the large chemical shift difference between gas phase and dissolved phase signal are such that a background free map of the tissue can be made in only few minutes. Compare to <sup>18</sup>FDG-PET and proton MR, HP xenon MR seems to be uniquely suited to detect BAT activity in overweight and obese individuals where the high lipid content of this tissue precludes its detection by proton MR methods and where the *in situ* presence of large fatty acid storage may preclude the need for an elevated glucose consumption.

**References:** [1]Nedergaard et al, Am J Physiol Endocrinol Metab 293(2) 2007; [2] Nedergaard et al, Ann N Y Acad Sci. 2010. [3] Hu et al, JMRI 31(5), 2010. & Branca et al MRM 65(2) 2011.