Detection of brown fat thermogenesis by hyperpolarized xenon gas MR

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Introduction: Brown adipose tissue is a fatty tissue specialized in non-shivering thermogenesis. BAT thermogenesis is currently hard to detect in adult humans since the tissue is located deep inside the body and the expected temperature increase upon stimulation of BAT is only a fraction of degree Celsius[1]. MR can be used to measure tissue temperature *in vivo*, but MR temperature measurements in fatty tissue are notoriously challenging. Our group has recently demonstrated direct imaging of BAT by HP Xenon gas MRI[2]. Xenon is highly lipophilic and the chemical shift of xenon dissolved in lipids is well known to have a linear temperature dependence [3]. In this work, we first examine the *in vivo* temperature dependence of the chemical shift of the 129Xe resonance dissolved in fatty tissues and then use this shift to demonstrate the feasibility to detect BAT thermogenesis *in vivo*.

Methods: All studies were conducted on a 9.4T small animal Bruker system using a surface xenon coil positioned above the interscapular BAT depot. For all xenon scans the animals were anesthetized with Nembutal, intubated and mechanically ventilated with a mixture of oxygen and natural abundance (26% 129Xe) xenon, hyperpolarized by SEOP up to 9.5% using a commercial polarizer (Polarean. Inc, Research Triangle Park, NC). To study the *in vivo* temperature dependence of the chemical shift of xenon dissolved in adipose tissue we used 4 female C57 ob/ob mice and 3 female Fisher rats, ranging from 4-8 weeks old. Bore temperature was regulated and maintained at different values from 35-25 ^{0}C, by an MR compatible heating system equipped with temperature control. Animal body temperature was monitored by an MR compatible rectal probe, and each animal was left to equilibrate to the outside bore temperature for about 10 minutes before each measurement. Spectroscopy experiments were then performed using an adiabatic pulse centered around 190ppm, with a TR=15s, and NA=16. For the detection of BAT thermogenesis, we used 5 lean and 6 obese mice, ranging in age from 4-8 weeks. Dynamic spectroscopy scans (TR=4s, NA=20) were acquired before and during stimulation of BAT by norepinephrine.

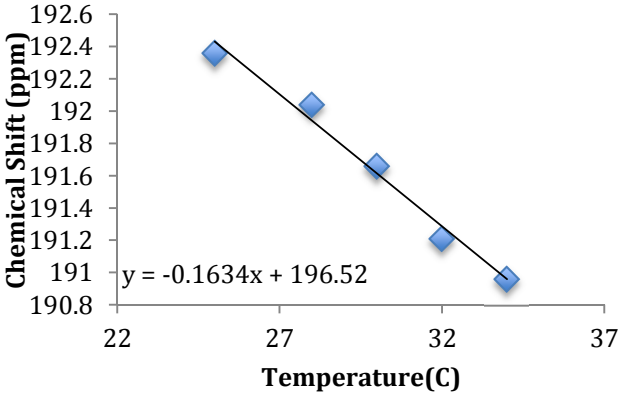

Figure 2 This chart shows the linear temperature dependence of the chemical shift of xenon dissolved in fat detected in an obese mouse.

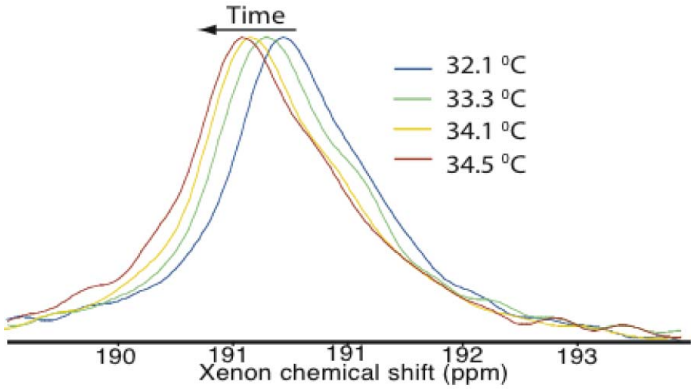

Figure 1 This figure shows the dynamic spectroscopy data acquired *in vivo* in an obese mouse upon adrenergic stimulation of BAT by norepinephrine. A clear frequency shift, corresponding to an increase in temperature of about 2 C over the course of about 8 minutes can be observed.

Results: The *in vivo* temperature studies reveal a linear temperature dependence of -0.16ppm/C between 25C and 37C of the chemical shift of 129Xe signal dissolved in adipose tissue. This linear dependence was the same in all animals examined. Studies on rats also have shown that, unlike the fat peak, the other resonance frequencies (129Xe dissolved in plasma and rbc) where not affected by the temperature changes, suggesting the feasibility of absolute temperature measurements by hyperpolarized xenon. Our *in vivo* BAT temperature studies revealed that this shift is enough to observe, in real time, the temperature increase (2 ^{0}C over a span of 8 minutes) that occurs in this tissue during adrenergic stimulation, with an accuracy of better than 0.2^{0}C. The temperature increase detected with xenon during adrenergic stimulation in BAT was also consistent with that detected in other animals using temperature probes located in their interscapular BAT.

Conclusions: Our experiments clearly show that hyperpolarized 129Xe MR can be used to detect BAT thermogenesis *in vivo* with an accuracy of better than 0.2 ^{0}C. Therefore, hyperpolarized xenon could be used to detect the small temperature increase that is expected in humans during adrenergic stimulation of BAT. Our data also suggest that hyperpolarized xenon can be used for measuring the temperature of tissues with high lipid content (e.g., breast or subcutaneous fat) with a much better accuracy than standard proton MR.

References: [1]Nedergaard et al, Ann NY Acad Sci 1212(1);[2]Branca et al, ENC Proceedings (2012);[3]Miller et al, PNAS(1981).