Oxygen-17 MRS for $CMRO_2$ measurements in the mouse brain at 16.4T

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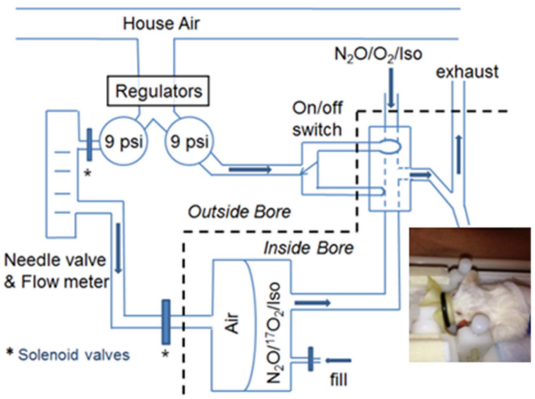
Introduction: To rapidly assess cerebral energetics *in vivo* in transgenic mouse models of neurological disease, a robust and quick method for quantification of cerebral oxygen consumption is needed. ^{17}O MRS methodology can be utilized to obtain cerebral metabolic rate of oxygen ($CMRO_2$) (1), and has been validated in rats (2) and cats (3). $CMRO_2$ is measured from an increase in the $H_2{}^{17}O$ signal above natural abundance that results from mitochondrial metabolism of $^{17}O_2$ gas inhaled over 2-3 minutes. Thereby the methodology produces 3D maps of $CMRO_2$ quickly and reliably. However, mice present unique challenges for ^{17}O MRS investigations due to their small size. First, oral intubation, which has been essential for controlled ^{17}O gas delivery in rats and cats, is substantially more challenging in mice. Second, minimization of the dead space between the ^{17}O reservoir and the mouse is required for rapid gas switching and accurate modeling of the time course of ^{17}O delivery. Critically, the detection sensitivity for the $H_2{}^{17}O$ signal increases in a supra-linear fashion with increasing magnetic fields (1). Here, we investigated the feasibility of ^{17}O MRS in mice without utilizing intubation at the ultra-high field of 16.4T.

Methods: MRI was performed using a 16.4 T Varian/Magnex (26cm bore) system and a home built $^1H/^{17}O$ surface coil (quadrature ^1H coil and a linear ^{17}O coil designed for minimal crosstalk). Healthy mice on FVB background were studied. An O_2/N_2O mixture (50:50) including 1-2% isoflurane was delivered by a newly designed gas delivery system (Fig. 1). ^{17}O MR spectra were acquired either with a pulse-acquire or a modified CSI sequence (TR=16 ms) (4). To acquire the time course of ^{17}O incorporation into H_2O, the delivered gas was switched to the $^{17}O_2$ /N_2O reservoir for 2.5 min.



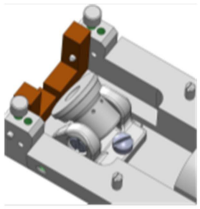


Fig. 1. *Gas delivery system.* A pneumatically remotely-controlled balloon switch determines which gas reaches the mouse: the ventilator provided isoflurane and normal O_2/N_2O mixture or a comparable mixture with $^{17}O_2$ from a gas-tight 2 chamber bag placed in front of the mouse inside the bore. Solenoid valves control delivery of air pressure to release the $^{17}O_2$ over 2-3 min. The tightly closed mouse nose cone (designed to allow flexibility in head angle, shown above) prevents leaking of $^{17}O_2$.

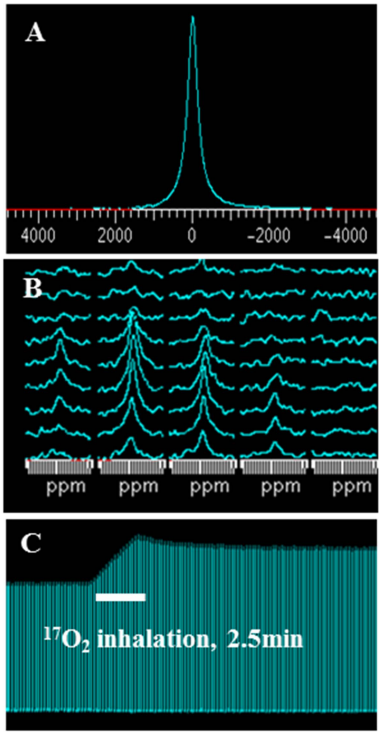


Fig. 2. A sample ^{17}O spectrum from the mouse brain with a pulse-acquire sequence (TR=16 ms, NEX=512); **b)** ^{17}O CSI of mouse brain (FOV= 20x20x10 mm^3, 9x9x5 phase encodes); **c)** time course of the $H_2{}^{17}O$ signal before, during and after a brief $^{17}O_2$ inhalation.

Results and Discussion: The sensitivity of the $^1H/^{17}O$ coil was first tested on the natural abundance $H_2{}^{17}O$ signals. The mean SNR of the surface coil localized $H_2{}^{17}O$ signal in the mouse brain was 281±12 (SD) with 8s acquisition (N=5) (Fig. 2a). Next, ^{17}O CSI images were acquired in healthy mice at natural abundance to demonstrate that SNR was sufficient to obtain 3D $CMRO_2$ maps (Fig. 2b). Finally, the newly designed gas delivery system was tested on the bench and inside the scanner to ensure good mouse physiology and no gas leak, both during delivery of regular O_2 and during the switch to the ^{17}O-labeled gas reservoir. $^{17}O_2$ was administered to demonstrate reliable measurement of the $H_2{}^{17}O$ time course in the healthy mouse brain (Fig. 2c). An oxygen consumption rate of 1.9 µmol/g/min was calculated (from the slope in Fig. 2c), in agreement with reported cerebral glucose utilization rates in the anesthetized mouse brain (5) assuming an oxygen-to-glucose index of 5.5.

In summary, ^{17}O MRS measurements of $CMRO_2$ in the mouse brain are feasible with high sensitivity using 16.4T, a surface $^1H/^{17}O$ coil and a newly designed gas delivery system. This method can be utilized to measure mitochondrial function in living mice quickly and repeatedly, without the need for oral intubation, and has numerous potential applications to study the involvement of energy failure in transgenic mouse models.

References: **1.** Zhu et al, *NMR Biomed* (2005) 18:83; **2.** Zhu et al, *JCBFM* (2007) 27:1225; **3.** Zhu et al, *JCBFM* (2009) 29:10; **4.** Zhu et al, *Neuroimage* (2012) 64C:437; **5.** Toyama et al, *J Nucl Med* (2004) 45:1398.

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