Novel application of Deuterium MRS: in vivo monitoring of glucose consumption

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Introduction Deuterium imaging and spectroscopy with ingested /injected D_2O bolus were published from the beginnings of MRI [1]. We report here preliminary results of a novel application of deuterium MR (DMR), namely *in vivo* and *ex vivo* monitoring of glucose consumption *via* measurement of *nascent mitochondrial water* after injection or ingestion of deuteriated glucose (cf. Figure 1). This work is motivated by the need to "see both sides of the coin" of mitochondrial function, namely the oxygen respiration and the glucose metabolic pathways that converge into the final, highly exergonic reaction of water formation. One can thus measure not only glucose, but also oxygen consumption without necessarily employing O-17 enriched air. Besides its immediate bio-analytical value, a long term aim of this project is to test consequences of the targeted deuterium isotope effect on enzymatic processes in healthy and diseased cells and to verify the hypothesis that this effect may be employed for treatment and monitoring of mitochondrial diseases [2].

Methods DMR measurements (AQ 0.2s; TR 0.3s; NS 128; LB 30; 38s/spectrum) were performed at 9.4 T on a wide bore (89 mm) Bruker Avance microimager equipped with a multinuclear probe. A set of experiments was performed on three male mice (C57/BL6) and another set, on *Tenebrio molitor* larvae. Mouse 1 (25 g), was injected *iv* with 8.9 mg deuteriated glucose *(ISOTEC)* dissolved in 0.4 ml saline solution; it was sacrificed after 1.5 hr and, after dissection, its whole body (except fur and skin) was placed in a 20 mm (maximum diameter available) NMR tube for running the DMR spectrum (shown in Figure 2, upper trace). Mouse 2 (32 g) injected *ip* with the same amount of glucose-d_7 as mouse 1 was sacrificed after 3.5 hr, and yielded the spectrum seen in the same Figure, second trace. Mouse 3 (26 g) gave the control (natural abundance) spectrum shown in Figure 2, third trace. *Tenebrio molitor* larvae were starved for several days, then placed in a 20 mm NMR tube together with food consisting of 0.4 g bran wetted with a aqueous solution of deuteriated glucose. Typical ^2H spectra are shown in Figure 3 together with a graph that displays the time evolution of the spectral line width (see Results and Discussion). The rate of metabolic HDO formation in larvae is shown in Figure 4.

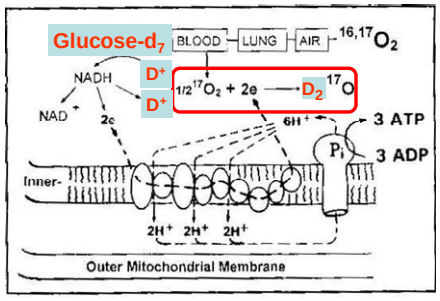

Figure 1

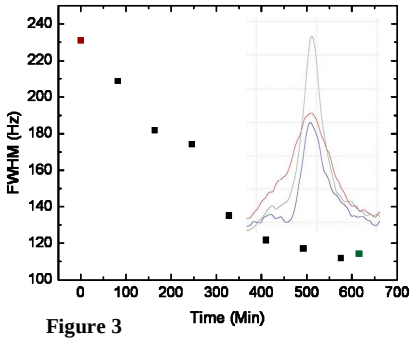

Figure 3

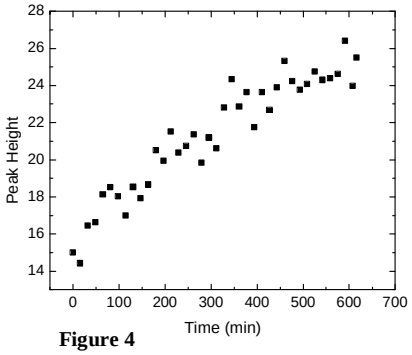

Figure 4

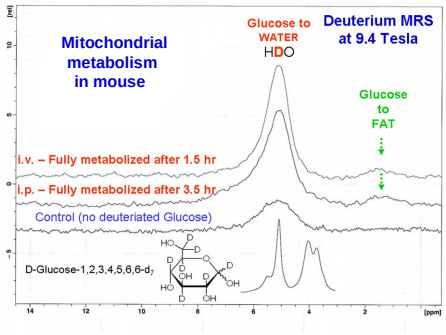

Figure 2

Results and Discussion In our approach the excellent tracer quality of deuterium (natural abundance 0.015%) is combined with the fact that only two well separated peaks are to be measured: that of nascent metabolic water, and that of the aliphatic chain of fatty acids. Thus, in spite of their large line widths (100-230 Hz) due to the electric quadrupole moment and unfavorable correlation times, the spectra can be interpreted in a quantitative manner. Figure 3 shows the natural abundance HDO peak of larvae that were not fed with glucose (lower, blue) trace; the middle (red) trace represents the spectrum obtained from larvae immediately after being mixed with bran containing deuteriated glucose; the upper (green) trace was recorded at the end of the experiment, when all glucose was metabolized into HDO (hence a line width similar to that of natural abundance HDO, but a much higher intensity due to the labeling of the nascent mitochondrial water). Interestingly, in contrast to mice, the larvae did not incorporate a visible amount of D-label into fat. Work is in progress to establish the best quantitation method.

References: 1. Ewy C, Ackerman J and Balaban R. Deuterium NMR cerebral imaging in situ. Magn Reson Med, 1988;8:35-44.
2. Kushner D, Baker A and Dunstall TG. Pharmacological uses of heavy water and deuterated compounds. Can J Physiol Pharmacol, 1999;77:79-88.
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