

Population-averaged 7T 1H MRS Determination of Metabolites in Human Skeletal Muscle at Rest

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Introduction

The concentrations of key metabolites in skeletal muscle are sensitive to genetic variations, diet, exercise and disease. For example, over accumulation of lipids within myocytes (intramyocellular lipids, or IMCL) has been linked to insulin resistance and type 2 diabetes (1). Abnormalities in carnitine, essential for oxidation of long-chain fatty acids, was found in skeletal muscle of patients with severe vascular diseases and mitochondrial encephalomyopathy (2). ¹H MRS offers many advantages for detection of these and other metabolites in patients, including oxidative fuels, metabolic intermediates, and other substrates related to muscle energy metabolism. However, reliable measurement of these metabolites in skeletal muscle can be quite challenging due to multiple factors intrinsic to MRS and skeletal muscle itself, including 1) overlap of resonances due to a limited frequency dispersion, 2) distorted spectral baseline and partial suppression of peaks from imperfect water suppression, 3) TE modulation of spin-coupled signals, and 4) resonance splitting and asymmetric lineshapes from fiber orientation and its dispersion (3). Consequently, a comparison of data across populations and over time requires standard, reproducible protocols for collection of MRS data. To overcome these technical barriers, we present here an optimized ¹H MRS acquisition protocol, termed “muscle module”, for acquisition of high-quality spectra for easy data analysis and hopefully improved the acceptance of MRS as a valuable diagnostic clinical tool. This muscle module is based on a STEAM sequence, which has less chemical shift displacement effect than PRESS, plus collection of spectra at two different echo-times, TE = 140 and 280 ms. This offers the advantage of better resolved IMCL and EMCL signals, minimal cross-contamination between taurine and carnitine, and optimized acetyl carnitine signal detection. As an additional advantage, this protocol does not require water-suppression (WS) preparation pulses, thereby lowering SAR exposure (4) and simplifying the scanning process. The improved spectral quality, in terms of enhanced spectral resolution and detection sensitivity for low abundance metabolites, was demonstrated in soleus muscle of a large group of healthy human subjects (n = 80 for TE 140 ms, a subset n = 50 for TE = 280 ms). Previously unknown metabolite peaks were easily detected in group-averaged spectra. Population-averaged spectra, with standard deviations, can be calculated from this large number of normal volunteers to create normative values and deviations, which can then be used with regression analysis to identify abnormal features in diseased patients.

Methods

The protocol was approved by our Institutional Review Board and informed consent was obtained from all participants (n = 80, mean age = 30.3 ± 9.0 yr, female 23, male 57). The left calf of each subject was placed on a customized 2-channel T/R partial volume coil with the leg oriented parallel to B₀. Localized single voxel ¹H MR spectra were obtained from the medial soleus muscle (typical voxel size: ~5 mm³) using a 7 Tesla Achieva scanner (Philips Medical Systems, Best, The Netherlands) and a STEAM sequence with TR = 2000 ms and TE = 140 (n = 80) and 280 ms (n = 50) without water-suppression. The resulting spectra were fitted using a Voigt lineshape in ACD software. [IMCL] was evaluated by comparison of the area of methyl signal at 0.87 ppm with the area of the total creatine methyl signal Cr3 at 3.02 ppm as internal reference (30 mmol/kg wet weight).

Results and Discussion

Two high-resolution ¹H spectra (TE = 140 ms and 280 ms) were collected from the soleus muscle of 50 out of 80 subjects from which a number of important metabolites including IMCL, EMCL, total creatine (Cr), total carnitine (Ctn), trimethylamine group (TMA), acetyl-carnitine (AcCtn), taurine (Tau) and carnosine (Csn) could be quantified (Fig 1). Of the assigned peaks, IMCL, Tau and AcCtn were best resolved from their neighboring resonances using a TE = 280 ms, whereas Csn, Ctn-TMA and Cr were more easily detected using a TE = 140 ms. One consistent feature seen in the TE = 140 ms spectra of these 80 healthy individuals is the near equality of the “twin peaks” from Ctn-TMA at 3.20 ppm and methyl group of total creatine (Cr3) at 3.02 ppm, with an intensity ratio of 1.00 ± 0.24 for TMA/Cr3 (n = 80). The concentration of IMCL, in mmol/kg wet weight, can be conveniently evaluated in the TE = 280 ms spectra from the intensity of its methyl signal at 0.87 ppm relative to Cr3, multiplied by a factor of 10, which assumes fixed [creatinine] and corrects for the different number of protons, 9, in the methyl groups of a triglyceride compared to creatine. For these 50 subjects, [IMCL] = 7.8 ± 3.4 mmol/kg ww, in agreement with a previous report (4). Interestingly, the acetyl signal of AcCtn at 2.13 ppm in resting muscle, although difficult to observe in most single spectra, is quite obvious in the summed spectra from either 50 (TE = 280 ms) or 80 (TE = 140 ms) subjects (Fig. 1a and 1b). The total scan time for the dual echo muscle module was about 9 minutes, which can be easily integrated into other MRI scanning protocols.

Conclusion We demonstrated that a “muscle module” consisting of collecting ¹H MRS at two different echo times can be useful to obtain highly reproducible ¹H spectra of skeletal muscle at 7T for accurate measurement of a number of metabolites. Deviations from these metabolite “norms” will provide a valuable indicator of altered muscle metabolism worthy of further investigation of the underlying (patho)physiology.

References 1. Machann J et al Diabetes Obes Metab 2004 6:239; 2. Brevetti G et al Circulation 1991 84:1490; 3. Khoo A et al 2009 61:16; 4. Ren J et al MRM 2010 64:662.

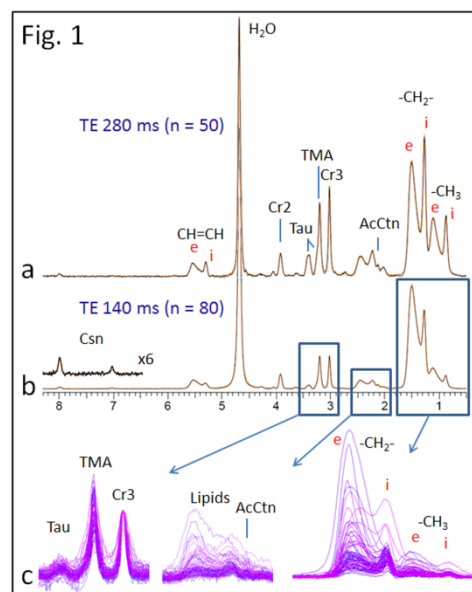


Figure.1. Hi-res 7T ¹H MR spectra from soleus muscle summed over either 50 healthy subjects (TE 280 ms) (a) or 80 healthy subjects (TE 140 ms) (b). The color traces in (c) show the spectra from each of 80 individuals.