Supplemental Digital Content 1

Complete methodology

Phosphorous Nuclear Magnetic Resonance spectroscopy (^{31}P NMR) protocol. A second set of experiments was performed to achieve intracellular pH and energy metabolism measurements in the following groups only: ADAPTED, NON ADAPTED AND STANDARD.

All localized *in vivo* 31P NMR experiments were performed on a 2.35 T 24 cm bore magnetic resonance imaging (MRI) / magnetic resonance spectroscopy (MRS) system (Biospec Avance, Bruker Biospin, Rheinstetten, Germany) with the use of a 1H and 31P dual 4 cm surface coil that was tuned with two excitation frequencies (100 MHz for 1H and 40.6 MHz for 31P). Spectra were obtained from the rat hind left leg tissues, mainly muscles (the signal was collected from all hind-leg muscles below the knee, and thus, only the averaged absolute values in the hind leg were assessed). A disadvantage of this procedure is surface tissue contamination of the spectra, its advantage being its simplicity.

Using 1H spectroscopy, the external magnetic field Bo was shimmed to the sensitive volume of the surface coil; the water line width (full width half maximum) was typically 10-15 Hz.

Phosphorous spectral parameters were as follows: single pulse sequence; radiofrequency pulse length, 50 μs; repetition time, 2 sec ; spectral width, 1500 Hz; number of averagings, 32; number of data points (time domain), 4096; zero filling to 16384. An exponential multiplication of 10 Hz line broadening was applied for apodization to suppress the noise level (Paravision, Bruker).

All of the *in vivo* 31P NMR spectroscopic data were transferred to a PC and processed with the Topspin data analysis package (Bruker). After Fourier transformation, the spectra were obtained and phased manually by zero and first order phase correction. The bone signal was filtered out by a second-order base-line correction.

An IDL-based, general-purpose curve-fitting package, called PAN (Peak Analysis, Dimeo, 2005) was adopted for quantitative calculations after export from Topspin. The primary features which prompted the choice of this software program were its ability to read multiple spectra at once and its method of determining the initial guess parameters (within PAN, these initial guesses are specified either by 'drawing' a model profile onto the data using the mouse or by numerically entering the initial guesses – this portion of the program was adapted to our NMR data). Thus, most of the spectra were treated in a fully automated approach by using available options for limiting the peak shift and width range used in fitting with upper and lower bounds or fixing the values.

With PAN, the peak area of phosphocreatine (PCr), and ATP ($\square$, $\square\square$ and $\square$ peaks), inorganic phosphate (Pi) and ATP and ATP ($\square$, $\square$ and $\square$ peaks) were obtained by simultaneously fitting to Lorentzian lineshapes using Marquart algorithm. The sugar-phosphate peak was observed sparsely and thus not measured (Figure 1).

Results were exported to Excel where only the relative peak areas are calculated, as the ratios of Pi/PCr, Pi/Sum of peaks, PCr/Sum of peaks and ATP/Sum of peaks, and where intracellular pH is calculated (^{31}P-NMR allows the measurement of the intracellular pH of the muscle through the shift of the frequency of the Pi peak relative to the PCr peak). The pH was calculated from the difference (δ_{obs}) of the fitted line positions of PCr and Pi with use of the following Henderson-Hasselbalch formula: $pH = 6.75 - \log[(\delta_{obs} - 3.35) / (5.60 - \delta_{obs})]$.

Ex vivo vascular reactivity measurements. After sacrifice of the animals by exsanguination at the end of conductance catheter study, the thoracic aorta and mesentery were removed and their vasoreactivity studied.

Vascular reactivity of aortic and mesenteric (radius 200-400 μm) rings was studied on a wire myograph (Danish Myo Technology, Arhus, Denmark) as previously described [22]. The

experiments were performed at 37°C in a physiological salt solution (PSS) with the following composition (in mM): 119 NaCl, 4.7 KCl, 14.9 $NaHCO_3$, 1.2 $MgSO_47H_2O$, 2.5 $CaCl_2$, 1.18 KH_2PO_4, and 5.5 glucose, continuously bubbled with 95% O_2 and 5% CO_2. After an equilibration period (at least 20 min) under optimal passive tension, two successive contractions in response to the combination of KCl depolarization (100 mM) and phenylephrine (10 ☐M) (Sigma-Aldrich, Saint Quentin Fallavier, France) were used to test the maximal contractile capacity of the vessels. After a 20 min washout period, concentration-response curves to phenylephrine were elicited by cumulative administration of this vasoconstrictor agonist (1 nM to 100 ☐M) to determine the same concentration producing an equal level of contraction in the different groups.