AMPLIFYING ATP MAGNETIZATION EXCHANGE EFFECTS BY BAND INVERSION TRANSFER: A 31P NMR STUDY IN HUMAN SKELETAL MUSCLE AT 7T

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INTRODUCTION: There is long-standing interest in measuring energy metabolism using ^{31}P magnetization exchange (ME) detected by saturation transfer (ST)[1-3]. One puzzling observation has been transfer from γ-ATP to β-ATP which has been attributed to the exchange: β-ATP ↔ β-ADP (since ADP may be co-saturated with γ-ATP) mediated by creatine kinase.[1] A recent study using ST suggested that the internuclear cross-relaxation, also known as nuclear Overhauser effect (NOE), is one of the mechanisms responsible for magnetization exchange[2]. The exchange phenomenon persisted in mice lacking creatine kinase and adenylate kinase, indicating that known biochemical pathways do not mediate the observed exchange. An alternative hypothesis holds that "invisible pools" or broad ATP resonances may be dispersed across the ^{31}P NMR spectrum and that these ATP resonances may be unknowingly saturated and detected later upon changes in the physical state of ATP. Recent studies in human calf muscle using inversion transfer demonstrated an equal magnitude of exchange transfer from γ-ATP to β-ATP, and from α-ATP to β-ATP. The ME effect, although small, is most consistent with ^{31}P-^{31}P NOE. Here, we explore a strategy to amplify this exchange effect at β-ATP by using a wideband inversion.

METHODS:

An adiabatic wideband 180° pulse was used to invert all major ^{31}P spins downfield of β-ATP, including Pi (4.9 ppm), PCr (0 ppm), γ- and α- ATP (-2.4 and -7.4 ppm) followed by a variable post-inversion delay period to allow for buildup of exchange effects at β-ATP before a hard-pulse readout. A series of ^{31}P spectra were acquired at 7T from human calf muscle of 5 healthy subjects (age 27.8 ± 4.8 y; BMI 22.1 ± 1.8) at rest. A partial volume ^{1}H/^{31}P coil was used for FID-based, non-localized ^{31}P detection. NMR sampling points 4 K, spectral width 8 kHz, post readout delay 25 sec, and number of average (NA) 4 scans.

RESULTS and DISCUSSION:

Upon wideband inversion of all downfield resonances from Pi to α-ATP, the intensity of β-ATP signal was decreased, depending on the delay, *t*, between the 180 pulse and the observe pulse (Fig.1a). The maximum reduction of β-ATP signal was 34.1 ± 3.2% (N = 5 subjects), occurring 1.4 sec after wide-band inversion (Fig.1b). This corresponds to a 4-fold increase in the effect as compared to the exchange effect, 8.3%, using frequency-selective inversion only at γ-ATP. The maximal β-ATP signal reduction occurred at a much later time (*t* = 1.4 sec) for wide-band inversion than for frequency-selective inversion of γ-ATP (*t* = 0.90 sec). Since this amplified effect and delay in maximal effect requires inversion at α-ATP, these observations cannot be due to effects on β-ADP approximately co-resonating with γ-ATP. An analysis of the wideband inversion data, based on Bloch-Solomon formalism for a 3-pool model (γ-ATP ↔ β-ATP ↔ α-ATP), yielded $T_{1,\gamma ATP}$ = 2.72 ± 0.09 sec, $T_{1,\alpha ATP}$ = 1.22 ± 0.06 sec, $T_{1,\beta ATP}$ = 1.19 ± 0.20 sec and cross-relaxation rate σ = 0.190 ± 0.006 s^{-1} for neighboring ATP spins. The relatively long $T_{1,\gamma ATP}$ is due to magnetization exchange effects between γ-ATP and the long-T_1 Pi and PCr spins[3], which markedly slows recovery of γ-ATP.

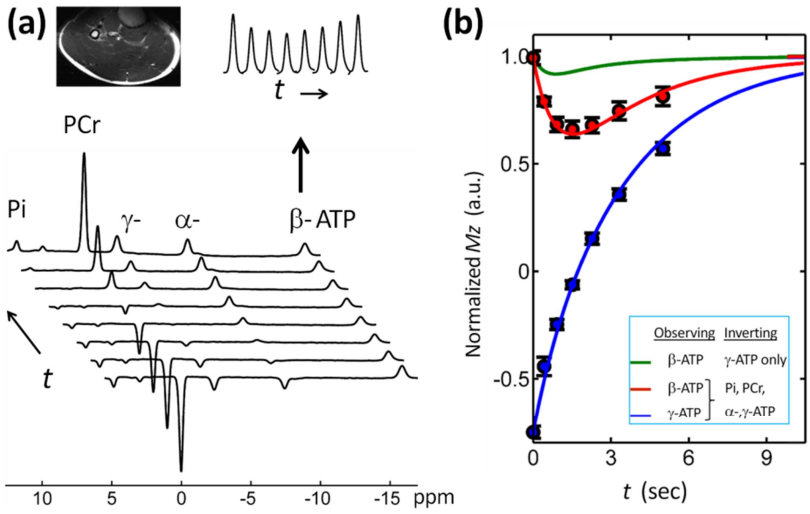

Fig.1 (**a**) ^{31}P MR spectra after wideband inversion at different delay times (*t*) with inset showing the ME effect at β-ATP due to NOE from α- and γ-ATP. (**b**) The plot of normalized z-magnetization against inversion delay time for β- (red) and γ-ATP (blue) under wideband inversion, with solid curves representing the fitting based on Bloch-Solomon formalism for a 3-pool model (γ-ATP ↔ β-ATP ↔ α-ATP), and compared to β-ATP ME under frequency-selective inversion (green,top trace).

CONCLUSIONS: Wideband ^{31}P inversion provides an effective strategy to enhance the ME effect within ATP, though the details of underlying biophysical mechanism is not clear. Given the physiological importance of ATP, further examination of these effects using independent model may be warranted.

REFERENCES: 1. Brindle KM, Radda GK, Biochim Biophys Acta 1985;829:188-201; 2. Nabuurs C, et al, J Biol Chem, 2010;285:39588-96. 3. Ren J, Yang B, Sherry AD, Craig MR, Magn Reson Med. 2014;DOI 10.1002/mrm.25256