Hepatic ATP synthesis rates in healthy humans

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Introduction

The human liver is the biggest internal organ and its various regulatory functions in metabolism are not yet fully understood. The chemical exchange rate between ATP and inorganic phosphate (Pi) is an important variable in hepatic energy metabolism that could reveal impairment of liver function in metabolic disorders.

^{31}P NMR spectroscopy offers the unique possibility of studying human energy metabolism non-invasively. The saturation transfer experiment [1, 2], in particular, allows quantification of the chemical exchange rate between Pi and ATP, i.e. ATP synthesis. One dimensional ISIS [3] in combination with a surface coil was used for localisation.

Methods

Six healthy male subjects were studied on a 3T (125.7MHz) whole body spectrometer (MEDSPEC, Bruker Biospin, Ettlingen, Germany) equipped with 45mT/m gradient system. A 10cm diameter linear polarised surface coil tuned to ^{1}H and ^{31}P frequencies was used, for transmission and reception of signal. The subjects were scanned in the supine position with the coil positioned over the lateral aspect of the liver. A 30mm slice was selected with a one-dimensional Image-Selected In vivo Spectroscopy sequence (ISIS) [3] with an adiabatic inversion pulse (WURST [4], 5ms, 3700Hz bandwidth).

To determine the equilibrium rate constant *k* of the ATP-synthesis, the γ-ATP resonance was selectively saturated using continuous wave irradiation. The signal (M_s) of inorganic phosphate (Pi) in the γ-ATP-saturation experiment was compared to the Pi signal (M_0) from a second experiment in which the saturation frequency was mirrored about the Pi resonance. Each scan comprised 256 averages with TR=2s. Four scans for M_s and M_0 were typically acquired. In addition, an inversion recovery experiment during γ-ATP saturation was performed to measure the apparent T_1-relaxation time. The equilibrium exchange rate constant was calculated as $k=1/T_1(1-M_s/M_0)$. The ATP-synthesis rate can then be calculated as the product of *k* and the concentration of Pi. [Pi] was quantified from unsaturated spectra relative to ATP peak area, with an assumed concentration of 2.5mmol/l liver tissue, an average value from many studies (eg. [5]).

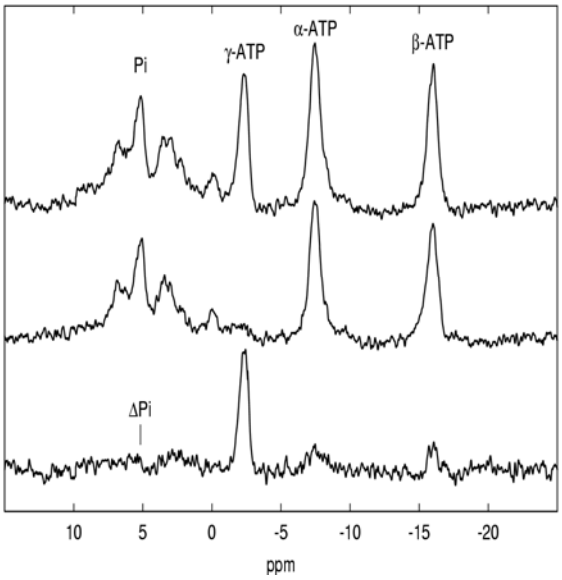

Illustration 1: Hepatic ^{31}P spectra acquired in 8.5min. No saturation (top), saturation of ATP (middle), difference spectrum (bottom).

Results

The localisation scheme used led to good tissue specificity and excellent SNR per unit time (see figure), enabling completion of the saturation transfer experiment within two hours. Mean values of $\Delta M/M=0.135\pm0.008$, $T_1=0.459\pm0.030 s^{-1}$ resulted in an equilibrium exchange rate constant $k=0.316\pm0.035 s^{-1}$. With [Pi]=1.62±0.072mmol/l the ATP-synthesis rates were 30.7±3.4mmol/l/min.

Discussion and conclusions

This study demonstrate the feasibility of ATP synthesis rate quantification in the human liver. These are, to our knowledge, the only published values of human hepatic ATP-synthesis. The precision of the experiment, limited by SNR, was around 30%. Agreement of human exchange rate constant k and rat data {$0.338\pm0.025 s^{-1}$ [6]} is excellent, both in value and precision . The experiment is sufficiently simple and reliable to enable future clinical studies that could yield valuable information on hepatic energy metabolism for clinical diagnostics.

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