Detection of prostate tumor metabolism using hyperpolarized [1-13C]-acetate

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Introduction

Prostate cancer is the most common cancer in the elderly men and the second leading cause of cancer death in men[1]. It has been known for many years that the metabolic fate of acetate in tumors differs from that in normal tissue. Recently the role of acetate has been recognized as probe of tissue metabolism trough entry into catabolic or anabolic pathways as mediated by Acetyl-CoA[2]. Prostate tumor as well as other cancers is characterized by altered energy metabolism and up-regulation of fatty acid synthesis[1, 3]. Here we report for the first time that hyperpolarized (HP) ^{13}C-acetate can be used to investigate prostate tumor metabolism through measurement of the tracer uptake and the metabolic conversion to Acetyl-carnitine (ALCAR) (fig. 1). The conversion to ALCAR was considerable low therefore it was necessary to develop a SNR optimal pulse sequence.

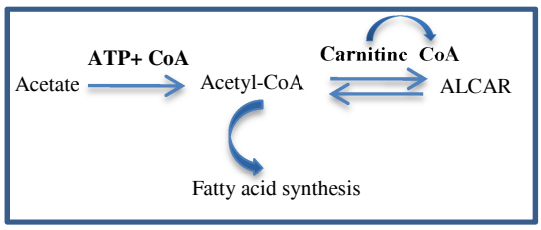

Figure 1: Once it is taken up by cells acetate is activated to Acetyl-CoA and it is converted to ALCAR a reservoir of activated acetyl units and a modulator of metabolic function.

Methods

[1-^{13}C]-acetate sodium salt was polarized in a 3.35T Hypersense DNP polarizer (Oxford Instruments, UK). Then the HP solution was injected into the rat tail vein inside the MR scanner (injected dose 5ml/kg; acetate concentration 130mM). All in vivo studies were performed on male Nude rats (n = 6) on a 3T GE HTX system equipped with a dual-tuned ^{1}H-^{13}C volume coil. All animals were injected subcutaneously in the neck region with PC-3 (human prostate cancer cells, 2x10^{6}). All of them underwent to MRI session one for ^{13}C spectra acquisition and the second one for ^{13}C MRI and uptake quantification. A spectral-spatial RF-pulse[4] (8 sublobes, duration 15,5ms, isodelay 7,0ms) was designed for exciting acetate and ALCAR separately. ALCAR was acquired with a higher flip angle in order to increase its SNR and additionally conserve the magnetization of the acetate pool. For ALCAR a flip angle of 20° was chosen, for acetate 5° with an alternating excitation with the two frequencies and a repetition time of 5s for each of them. The measurement started 2s after injection of the substrate a 12mm slice containing the whole tumor was excited. Spiral imaging (FOV 8cm; real resolution 5mm) after the described SPSP excitation was used to detect acetate tumor uptake with FA=15°; TR=2s. For ALCAR imaging each image was acquired every 6s, with three spiral ideal encoding steps (ΔT_E = 1.2 ms; FA= 33°; 44°; 90°) in order to separate the ALCAR signal from the acetate rest signal.

Results and discussion

The spectra time evolution of HP acetate (182.5 ppm) and its metabolic product ALCAR (174.5 ppm) recorded in the tumor slice of an exemplary dataset are shown in Fig. 2. In all animals increased [1-^{13}C]-acetate signals in the tumor area could be detected by simple display of integrated [1-^{13}C]-acetate images with corresponding Fast Spin Echo anatomical images (Fig. 3a). ALCAR SNR in the tumor region was too small for imaging purpose. In order to define the time evolution of acetate signal and detect the agent uptake one region of interest was drawn in the tumor and one in the blood vessel (Fig. 3b). Higher uptake in tumor region was clearly visible.

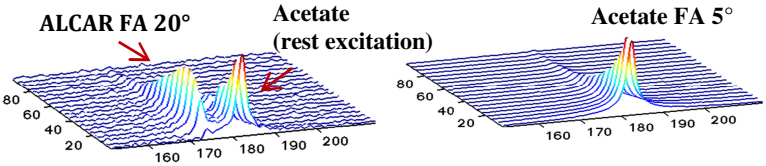

Figure2: In vivo ^{13}C spectra recorded in the tumor slice following the injection of hyperpolarized acetate. Left spectrum: ALCAR excitation; in the spectrum the rest excitation of HP acetate is still visible due to pulse imperfection. Right spectrum: Acetate excitation.

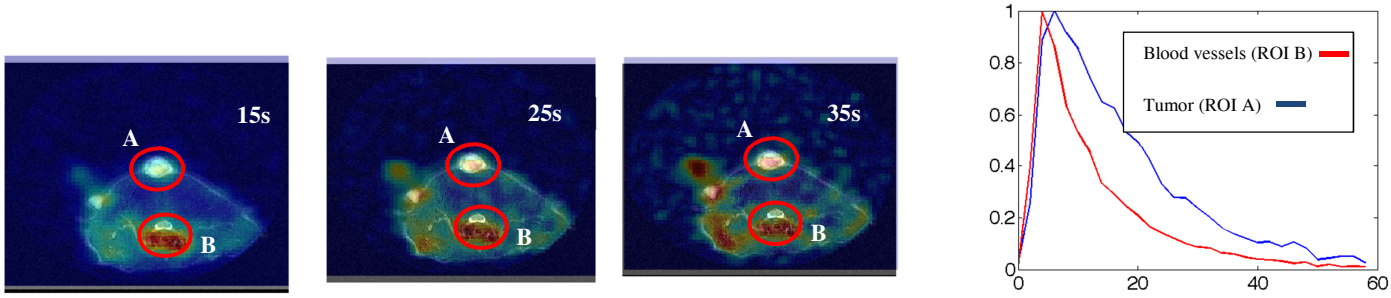

Figure 3: a) On the left are shown ^{13}C acetate images over ^{1}H FSE at different time steps. An increase by time of acetate uptake is detectable. One region of interest was drawn to delineate the tumor region (A) and one for the blood vessel (B). b) On the right side is shown the time evolution of acetate signal in the regions of interest A (tumor) and B (blood vessels).

Conclusion

This study reveals that the visualization of prostate cancer with HP ^{13}C-acetate is feasible in rats. Such baseline data could be important when following the modifications in metabolism and to monitor FAS expression in prostate cancer. Further investigations have to be done to evaluate the possibility to correlate cancer aggressiveness with quantitative analysis of prostate cancer metabolism and HP 13C-acetate tumor uptake.

References

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