Drug Distribution Imaging of Anticancer Drug 5-FU Using $^{19}F/^{1}H$ Double-Tuned RF Coil

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Introduction

^{19}F MRI/MRS has been used in drug distribution studies of the anticancer drug 5-fluorouracil (5-FU) and other ^{19}F-labeled compounds [1-3]. Together with ^{19}F imaging, acquisition of ^{1}H images are helpful to obtain anatomical information. A $^{19}F/^{1}H$ double-tuned RF coil is suitable for acquiring ^{19}F and ^{1}H images at the same time. The double-tuned RF coil facilitates imaging workflow of two nuclei, since it is not necessary to retune the RF coil during the experiment. Additionally, the coil makes it possible to correct the measured ^{19}F data using the obtained ^{1}H data. However, conventional double-tuned RF coils have higher signal loss in two contiguous frequencies (especially with the combination of ^{19}F and ^{1}H). Therefore, we have developed and reported a highly sensitive $^{19}F/^{1}H$ double-tuned RF coil [4]. The sensitivity of this coil was more than two times higher than that of the conventional double-tuned RF coil. In this study, we demonstrate imaging of anticancer drug 5-FU and its metabolite distribution using the developed double-tuned RF coil at 7 T.

Materials and Methods

5-FU is a metabolic antagonist that is converted into active metabolites (fluorinated nucleosides and nucleotides, Fnuc) and catabolites (α-fluoro-β-alanine, FBAL) in cells by enzymes. These substances contain one fluorine atom in each molecule and have different chemical shifts. We conducted an experiment on a 7-T MRI (MRI System, Varian, USA) using the developed double-tuned transmit/receive solenoid RF coil. The coil dimensions were 140 mm in length and 65 mm in diameter, and it was tuned to resonant frequencies at 7 T of ^{19}F = 282 MHz and ^{1}H = 300 MHz.

In the animal study, female Wistar rats bearing Walker 256tumor were used (body weight 190 g). The rats were anesthetized with 2-4% isoflurane administered in combination with 30% O_2 through a mask. Initially, ^{1}H was measured using the spin echo, FOV of 200 × 200 mm^2, matrix size of 256 × 256, 2-mm slicing, and TR/TE = 1000/12 ms. Next, 250 mg/kg of 5-FU (Kyowa Hakko Kirin, Japan) was bolus-injected intravenously. Thereafter, ^{19}F was measured cyclically to obtain the time course using the fast spin echo with frequency selective pulses of 3-ms Gaussian-shaped pulses, FOV of 400 × 100 mm^2, matrix size of 64 × 16 without slicing, TR/TE = 1000/7 ms, and ETL = 4. Chemical shifts of 5-FU and its metabolites were selected and interleaved within the TR: +5 ppm for Fnuc, 0 ppm for 5-FU, and -19 ppm for FBAL. The total measurement period was about 4.5 hours. The animal was kept in the same position during the entire experiment. 5-FU and FBAL images were obtained by the 10-minute average value. Fnuc images were obtained by the 20-minute average value.

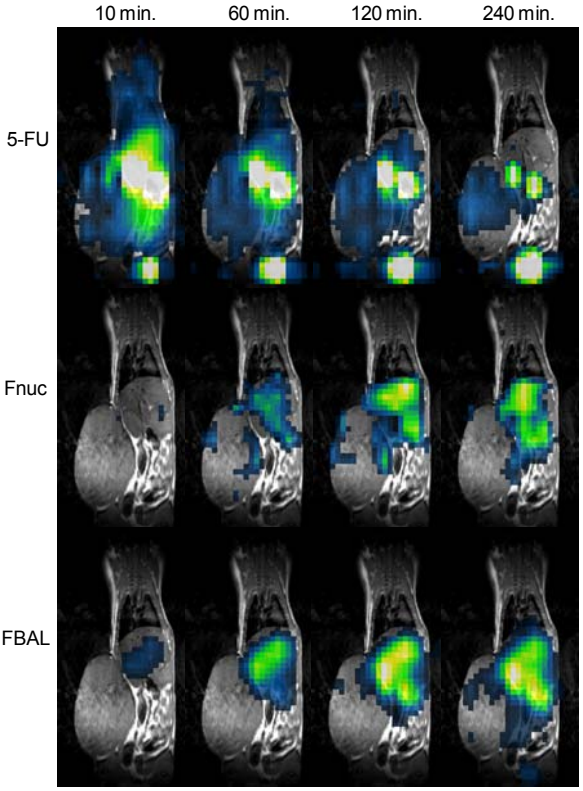

Fig. 1 Time course of 5-FU and its metabolites in rat bearing Walker256 tumor after bolus injection of 5-FU.

Results and Discussion

Figure 1 shows a time course of 5-FU, Fnuc, and FBAL distribution, which was overlaid onto the ^{1}H image of the rat. It clearly demonstrates the different distributions of the 5-FU, Fnuc, and FBAL in different organs and tissue, such as tumor, liver, kidney, stomach, and bladder. The spatial changes in the signal intensity between several images may be used to understand the pharmacokinetics. The mean signal intensities were calculated for several regions of interest such as tumor tissue and liver (Fig. 2). This graph shows that the signal intensities of 5-FU and FBAL dramatically changed during the study. These results show that 5-FU was metabolized to FBAL largely in the liver. The signal intensity of 5-FU at the center of the tumor was almost constant during the whole experiment over 240 minutes. The metabolic rate from 5-FU to Fnuc or FBAL was very slow in the center of the tumor. This result indicates that the center of the tumor was not very active. Fnuc was detected at the anticipated position at the rim of the tumor, stomach, liver, and kidney. These images indicate that 5-FU was metabolized to Fnuc in the tumor and stomach. The accumulation of Fnuc in the liver and kidney was attributed to the metabolite excretion. These results suggest that this double-tuned RF coil will be a powerful tool for ^{19}F distribution imaging and pharmacokinetics research.

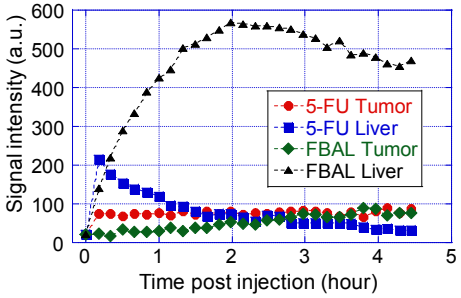

Fig. 2 Plots of signal intensities of 5-FU and FBAL in tumor tissue and liver.

Conclusion

We demonstrated that the double-tuned RF coil can be used to obtain 5-FU distribution images of a rat. We obtained active metabolite and catabolite distribution images with administered drug distribution images at the same time using fast spin echo with frequency selective pulses. The results indicated that the developed double-tuned RF coil will be a powerful tool for pharmacokinetics research.

Reference

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