Effects of Ischemia-Reperfusion Injury on ^{23}Na Relaxation Times and its Implications on Quantification of Corticomedullary Sodium Concentration by ^{23}Na MRI

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INTRODUCTION

The maintenance of the corticomedullary sodium gradient, an indicator of normal tubular function in the kidney, is presumably lost early in the course of acute tubular necrosis (ATN) [1]. Ischemia remains the major cause of ATN in the adult population. ^{23}Na MRI has been applied to study the alterations in renal sodium distribution in the rat kidney during ischemia-reperfusion (IR) injury [2]. The observed changes in ^{23}Na MRI signal intensity (SI) of the renal medulla and cortex during ischemia and reperfusion can be caused by a) a change in sodium concentration, and/or b) changes in ^{23}Na relaxation times. In this study, ^{23}Na MRI and MRS are applied to evaluate the effects of renal ischemia and reperfusion on ^{23}Na relaxation times in renal medulla and cortex, and the changes in [Na^+] due to IR injury are quantified by applying T_1 and T_2 corrections.

METHODS

^{23}Na MRI: All ^{23}Na MR experiments were performed on a Varian 9.4-Tesla, 31-cm horizontal bore system equipped with a 12-cm gradient insert. Effect of ischemia and reperfusion on ^{23}Na MRI SI was investigated in Wistar rats (n=5) using a home-built 50 mm diameter loop-gap resonator tuned to 105.9 MHz. A 10 mm diameter tube containing 50 mM NaCl was positioned next to the rat and used as a signal intensity reference. A 3D ^{23}Na gradient-echo (GE) imaging sequence with the following parameters was used: 50 ms repetition time (TR), 4.5 ms echo-time (TE), 64 × 64 × 16 data matrix over a field of view of 6 × 6 × 6 cm. Weighted signal summation (WSS) was used to improve SNR. On average, 9.67 transients were collected per phase-encoding step. ^{23}Na images were collected every 10 minute during baseline, 50 min ischemia and 50 min reperfusion periods. In-magnet ischemia was induced by a snare taut placed around the vascular pedicle of the left kidney. High-resolution ^{1}H images were collected for anatomical delineation of kidney regions using a 2D multi-slice spin-echo (SE) sequence and following parameters: 2000 ms TR, 30 ms TE, 256 × 256 × 16 data matrix over a 60 × 60 × 60 mm FOV.

T_1 and T_2 Measurements using MRS: ^{23}Na fast and slow T_2 (T_{2f} and T_{2s}, respectively) and T_1 of the whole kidney were measured by MRS on separate cohort of rats (n=4) using a 10-mm-diameter surface coil directly placed on exposed kidney. ^{23}Na T_1 was measured using a pulse-burst saturation recovery pulse sequence consisting of 10 saturation pulses followed by an incremental delay (16 values ranging from 0.05 to 200 milliseconds), a 90° observed pulse and acquisition with Cyclops phase cycling. ^{23}Na T_{2f} and T_{2s} were measured using a Hahn SE sequence consisting of a composite 180° pulse. The TE was varied from 0.06 to 40 milliseconds. The instrument dead time of 10 microseconds was included as a part of the TE. A pair of T_1 and T_2 data was collected every 15-16 min during normal perfusion, 50 min ischemia and 50 min reperfusion. The relaxation times were computed by fitting a plot ^{23}Na resonance area versus TR or TE to a mono-exponential function for T_1 and a bi-exponential function for T_2.

T_1 and T_2^* Measurements using MRI: T_1 and T_2^* of renal cortex and medulla were measured by ^{23}Na MRI on two additional cohort of rats (n=3 each) using the 50 mm diameter loop-gap resonator. A 3D GE imaging sequence with similar imaging parameters as describe above was used. For T_1 measurements, the image matrix size was reduced to 64 × 32 × 8 and five ^{23}Na images were collected with a 4.5 ms TE and 10, 20, 50, 80 and 120 ms TR. T_1 measurements were repeated every ~16 min during normal perfusion, 50 min ischemia and 50 min reperfusion. T_1 of the medulla and cortex was computed by least square fitting the SI of the regions of interest (ROI) to a mono-exponential function. For T_2^* measurements, the image matrix size was reduced to 64 × 32 × 8, the readout gradient was increased by a factor 10 to allow shorter TE and ten ^{23}Na images were collected with a 50 ms TR and 1.5, 2.2, 3.5, 4.5, 6, 8, 11, 15, 19 and 25 ms TE. T_2^* measurements were repeated every ~25 min during normal perfusion, 50 min ischemia and 50 reperfusion. Least squares curve fitting of the T_2^* image data to a bi-exponential function did not give a reproducible value for T_{2f}^* because the T_{2f} in tissue is very short. Thus T_{2f} and the relative fractions of the fast and slow components for the whole kidney from the spectroscopy experiments were used to calculate T_{2s}^* of the cortex and medulla by bi-exponential curve fitting of SI.

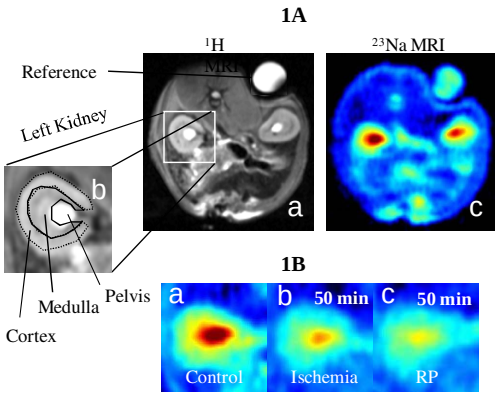

Fig. 1A. ^{1}H and ^{23}Na Magnetic resonance imaging (MRI) of the rat kidney. (a, b) A transaxial projection of a ^{1}H MRI and zoomed left kidney image with applied ROI's of medulla, cortex and pelvis (c) A transaxial projection of a 3-D ^{23}Na MRI corresponding to ^{1}H MRI represented in (a). Fig. 1B. Zoomed ^{23}Na MR images of a kidney collected during (a) baseline, (b) after 50 min of ischemia and (c) after 50 min of reperfusion.

RESULTS

Fig 1A shows a transaxial slice from a ^{1}H MRI and a zoomed left kidney image with ROI's for medulla and cortex. A transaxial slice from a 3-D ^{23}Na MRI corresponding to ^{1}H MRI is represented in (A). Fig 1B shows zoomed ^{23}Na MR images of a kidney collected during baseline, after 50 min of ischemia and after 50 min of reperfusion. After 50 min of ischemia the average ^{23}Na SI relative to the reference decreased from 1.57 ± 0.03 to 1.09 ± 0.03 in the medulla and from 0.92 ± 0.06 to 0.74 ± 0.04 in the cortex. The corticomedullary sodium SI ratio decreased from 1.59 ± 0.02 to 1.23 ± 0.06 after 50 min of ischemia; on 50 min of reperfusion the ratio continued to decrease and plateaued at 1.213 ± 0.05. Results of both MRS and MRI experiments showed that the T_1 of renal medulla (36 ± 3 ms) and cortex (38 ± 1 ms) are similar in normal kidney. After 50 min of ischemia the T_1 of medulla (29 ± 3 ms) and cortex (30 ± 3 ms) decreased to similar values. The T_1 of both the kidney compartments recovered slightly after 50 min of reperfusion. ^{23}Na T_2 measurements by MRS showed that T_{2s} and T_{2f} of normal kidney are 28.4 ± 0.6 and 3.2 ± 0.1 ms, respectively. Both T_{2s} and T_{2f} of the whole kidney decreased to 22 ± 2 and 1.9 ± 0.1 ms, respectively, after 50 min of ischemia. Both the relaxation times recovered slightly after 50 min of reperfusion. The relative contribution of the fast and slow relaxation components was 25:75 (fast: slow) before ischemia, 33:67 after ischemia and 34:66 after reperfusion. This ratio is approximately reversed compared to the theoretically expected 60:40 ratio for a bi-exponentially relaxing sodium in a homogeneous sample. Regional ^{23}Na T_2^* measurements by MRI showed that T_{2s}^* of cortex and medulla are 19 ± 1 and 18 ± 1 ms, respectively. These relaxation times are shorter than the T_2 of the whole kidney measured by MRS because of B_o inhomogeneity effects. The T_{2s}^* of both medulla and cortex decreased to 13 ± 1 ms after 50 min of ischemia and recovered to 15 ± 1 ms after 50 min of reperfusion. The changes in T_1 and T_2^* with ischemia and reperfusion caused ~ 15 % decrease in ^{23}Na MRI SI during ischemia and reperfusion. The effect of ischemia and reperfusion on medulla and cortex [Na^+] was calculated using the ^{23}Na SI of the tissue relative to the 50 mM reference and the sodium relaxation time. Ischemia for 50 min decreased the TSC by ~18 % and ~16 % in medulla and cortex respectively. TSC in medulla did not recover after 50 min of reperfusion but the cortex TSC was recovered.

CONCLUSION

Renal ^{23}Na MRI revealed a marked decrease in medulla and cortex ^{23}Na MRI SI during the early evolution of ATN caused by ischemia-reperfusion injury. ^{23}Na relaxation time measurements by MRI and MRS showed that sodium relaxation characteristics are similar in renal medulla and cortex in normal kidney. Ischemia causes a significant decrease in the relaxation times which affects the calculation of medulla and cortex [Na^+] from MRI SI data. However, the changes in relaxation times for the medulla and cortex are identical, thus the medulla to cortex ^{23}Na SI ratio represents [Na^+] ratio in the two compartments during ischemia and reperfusion.

REFERENCES

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