Sodium Renal Imaging in Mice at High Magnetic Fields

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This work presents the first sodium MRI functional renal study on a mouse model. The tissue sodium concentration was monitored during induced diuresis with furosemide. By using density-weighted chemical shift imaging (DWCSI) at high field strength a temporal resolution of less than 5 min for three dimensional (3D) data sets with high spatial resolution was achieved. A maximum increase of 20% in the cortex and a decrease of 45% of the original signal strength in the medulla were observed. These findings correspond well with experiments conducted on much larger rodent models. Magn Reson Med 58:1067–1071, 2007. © 2007 Wiley-Liss, Inc.

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Since the first studies performed in the early 1980s (1) renal MRI has become an increasingly useful tool for clinical diagnosis. Today, it allows for a comprehensive examination of almost the complete spectrum of urologic diseases (2). Functional parameters such as glomerular filtration, tubular concentration and transit, blood volume and perfusion, diffusion, and oxygenation can be measured noninvasively with MRI (3). Many studies have been performed on animal models to investigate, for example, essential hypertension linked to kidney malfunction in rats (4,5). In addition to proton MRI, sodium MRI has a large potential role to play in the diagnosis of renal disease, since sodium plays a major role in fluid and electrolyte homeostasis with the extracellular corticomedullary sodium concentration gradient regulating fluid homeostasis. This concentration gradient is the driving force behind the reabsorption of water from the filtrate back into the plasma.

Relatively few examples of human sodium renal images have been published (6,7). In one of the most recent studies, Maril et al. (7) studied the effect of dehydration on sodium concentration in human kidney, showing that the concentration gradient from the cortex to the medulla increases by ~25% after 12 h of water deprivation. Animal studies using sodium imaging have been more prevalent, with the first experiments having been performed on rabbits and guinea pigs, and recent studies using rats (8–10).

Since the mouse has become the most important animal model for human disease, an important step is to determine the feasibility (in terms of spatial and temporal resolution as well as signal-to-noise ratio [SNR]) of sodium MRI to image the murine kidneys under “static” conditions, as well as to monitor dynamic changes of the sodium concentration during challenges such as induced diuresis induced by furosemide. Furosemide is a loop diuretic that blocks the Na⁺/K⁺/Cl⁻ cotransporter in the apical membrane of the thick segment of the medullary ascending limb (11) with a concomitant “washout” of sodium in the medulla. The cortical total sodium concentration is also known to increase during this process (12). Furosemide administration is a commonly used functional model, employed for example by Maril et al. (8), who conducted a dynamic study in rat kidneys (13,14). In addition to the normal challenges of sodium imaging (a significant short T₂ component, low gyromagnetic ratio and concentration relative to protons), the physical size of the murine kidney is very small, even compared to other rodents. To maximize the SNR a variety of short-echo imaging techniques have been used to acquire data with minimal T₂ loss (15–18). In this study, we used a three-dimensional (3D) pure phase-encoding sequence, with nonlinear k-space coverage. The technique is referred to as density-weighted chemical shift imaging (DWCSI) (13,19), and has been used previously for sodium imaging of the mouse heart (14).

MATERIALS AND METHODS

Proton and Sodium MRI Experiments

Experiments were performed on a Bruker 17.6 T wide bore magnet (89 mm diameter, 750 MHz proton frequency, 198 MHz sodium frequency) with an Avance console. The spectrometer is equipped with two gradient systems for imaging. The MINI 0.5 gradient system has an inner diameter of 57 mm and a maximum gradient strength of 200 mT/m, and was used for proton imaging. The stronger MICRO 2.5 gradient system has a maximum gradient strength of 1 T/m and 40 mm inner diameter, and was used for sodium data acquisition. The transmitter for the proton experiments has a maximum power output of 300 W and the transmitter for sodium 500 W.

Animals

All experiments were performed on healthy adult NMRI mice (Charles River, Sulzfeld, Germany) with a weight between 20 and 30 g. The mice were anesthetized with a mixture of carbogen and isoflurane (1.5%). To monitor the health state of the mouse a cardiac- and respiratory-monitoring unit (RAPID Biomedical, Wuerzburg, Germany) was used. Altogether, six animals were used for these studies.

RF Coils

For the proton scans a commercial linear birdcage resonator was used (Bruker, 38 mm diameter, eight legs, 50 mm

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Density-Weighted Sodium Chemical Shift Imaging

The \( k \)-space sampling points of the 3D phase-encoded sequence are calculated from the total number of points to be acquired, the nominal spatial resolution desired, and a radial weighting function (13,19). A total of 8192 \( k \)-space data points were acquired, with 256 complex time-domain points per free induction decay (FID), and one signal average. Data processing was performed with Interactive Data Language (IDL; Boulder, CO, USA) software running on a Linux PC platform. Zero-filling by a factor of two was applied in all four dimensions. After applying an exponential filter (10-Hz line-broadening) the FIDs were Fourier transformed, and reordered onto a 128 \( \times \) 128 \( \times \) 128 Cartesian grid (19). Finally, sum-of-square images of the sodium peak in the spectral dimension were calculated. Although a direct comparison of DWCSI and more conventional sodium imaging techniques (15) was not performed, the very short echo-time and constant-time imaging nature (which eliminates \( T_2^* \)-induced image blurring) are the major advantages of this type of sequence.

FIG. 1. (a) A coronal slice from a 3D gradient echo data set of the kidneys of a mouse. Spatial resolution = 230 \( \times \) 170 \( \times \) 170 \( \mu \)m\(^3\), total data acquisition time = 16.5 min, TE = 1.7 ms, TR = 60 ms, and flip angle = 15\(^\circ\). (b) A slice from a multislice RARE data set from a different mouse. In-plane resolution = 125 \( \times \) 256 \( \mu \)m, slice thickness = 500 \( \mu \)m, RARE factor = 8, effective echo time = 23.1 ms, TR = 4 s, signal averages = 4, and total data acquisition time = 7 min.

FIG. 2. (left) Coronal slice and (right) axial slice from 3D DWCSI data sets of mice kidneys with a spatial resolution = (1.5 mm\(^3\)), phase encoding steps = 8192, TR = 281 ms, TE = 0.46 ms, spectral width = 4000 Hz, complex time-domain points = 256, signal average = 1, and total data acquisition time = 38.4 min.
from a 3D gradient echo sequence: the two kidneys with some of the blood vessels are clearly distinguishable. In order to improve the corticomedullary contrast within the kidney, a rapid acquisition with relaxation enhancement (RARE) sequence was used on a second mouse. Figure 1b shows that the renal pelvis, structures in the medulla, and the cortex are all distinguishable. Since these images are purely for locating the kidneys, no attempt was made to optimize the data acquisition parameters for maximum contrast-to-noise ratio. In all of the animal studies, proton images were acquired only once, i.e., they did not form part of the dynamic studies, in order to assess the physical dimensions and locations of the murine kidneys, and also to aid in design of the sodium RF coil.

Figure 2 shows images acquired using 3D sodium DWCSI results at an isotropic resolution of 1.5 mm, using 8192 phase-encoding steps. The TR was set to be much higher than the $T_1$ value of both cortex and medulla (see below) to avoid saturation effects. The kidneys and major blood vessels are easily seen, and there is considerable contrast between the medulla and cortex of both kidneys. Four profiles from the left kidney with the corresponding axial images at different positions are shown in Fig. 3. The signal can be assigned to the cortex (a), the medulla and the pelvis (b), and a mixture of the afferent and abducent blood vessels and the ureter (c). While the sodium signal increases from the outer cortex to the outer medulla by a factor of three, the increase from the outer cortex to the inner medulla and the pelvis is about a factor of six. These images do not show the simple linear gradient from the outer cortex to the inner medulla reported in rat studies (8), but rather a more complicated concentration profile. The maximum signal intensity corresponds to the inner medulla and the pelvis: this hypertonicity is due to the accumulation of fluid in the interstitium as well as in the structures of the medulla, including the loops of Henle, the urine collecting ducts, and the vasculature.

Using the inversion-recovery 3D DWCSI sequence the measured $T_1$ value was $41 \pm 4.0$ ms in the cortex and $67.9 \pm 1.3$ ms in the medulla. This result shows a clearly elevated $T_1$ in the medulla of the kidney, which might be due to the higher mobility of the sodium cations in this region of the kidney. This value is about 20% higher than the $T_1$ reported in rat kidneys at 4.7 Tesla (8), although the authors do not discuss in detail their measurement method. The long time-constant $T_2$ values were measured to be $29.2 \pm 3.8$ ms for the cortex and $36.1 \pm 2.8$ ms for the medulla, respectively. The fast $T_2$ time-constant of the bilinear fit were $0.8 \pm 0.6$ ms for the cortex and $1.0 \pm 0.6$ ms for the medulla region.

Changes in the renal sodium distribution during administration of furosemide were monitored using images obtained with a temporal resolution of 4 min 40 s. To achieve this temporal resolution the TR was shortened to $34$ ms. The flip angle used was reduced accordingly to maximize the SNR and minimize saturation effects from the different $T_1$ values of cortex and medulla. A total of 12 axial slices at different time points, one before and 11 after injection of
Furosemide, are shown from (a) to (l) in Fig. 4. A significant decrease in the sodium signal in the medulla and an increase in the renal cortex are evident. Figure 5 shows the profiles along the corticomedullary axis (the bar shown in Fig. 4a). A total of 15 min after the bolus injection the sodium signal in the renal cortex is about 20% above its initial level. At 30 min later, however, the signal is actually below that measured before the administration of furosemide. The sodium signal in the medulla, in contrast, decreases to about 55% of the initial signal after approximately 25 min (Fig. 5f and g). During the next 25 min the signal intensity of the medulla remains essentially unchanged. This decay of the signal in the medulla was fitted to an exponential decay function with a time constant of $6_{\pm1}$ min: this value is in good agreement with that reported by Maril et al. (8) in rats. Furosemide is known to have two main effects on the sodium concentration in the kidney. Due to the inhibition of the absorption of $\text{Na}^+$ and $\text{Cl}^-$ in the macula densa cells and the following reactions, the total sodium concentration increases in the kidney (12). The second effect takes place in the medulla, where the cotransport of $\text{Na}^+/\text{K}^+2\text{Cl}^-$ is inhibited and the reabsorption of $\text{Na}^+$ and $\text{Cl}^-$ is reduced, resulting in a lower total sodium concentration (20). The changes in signal intensity in the data sets shown in Figs. 4 and 5 do indeed show such effects.

CONCLUSIONS

The results presented here demonstrate that sodium imaging of renal morphology and function is possible using high magnetic fields and data acquisition sequences that are designed for short echo times and efficient $k$-space coverage. Measurement times of the order of $\sim5$ min can give sufficiently high SNR with a high spatial resolution for quantitative analysis. In these experiments an external standard was not used, which would have allowed direct calculation of sodium concentration. However, given that the quadrature $B_1$ field was measured in phantoms to have less than a 5% variation over the volume of the kidneys, that the $T_1$ is the same for both intra- and extracellular sodium (commonly assumed), and that there is minimal loss of intracellular signal since the $TE < < T_2$ for the short component, there is a linear relationship between the measured signal intensity and sodium concentrations. Indeed the profiles in Fig. 3 agree with values from the human literature in which sodium concentrations in the inner medulla, outer medulla, and cortex are approximately in an 8:3:2 ratio. These results suggest that meaningful sodium experiments can be performed on transgenic mouse models of disease, complementing the recent advances in sodium imaging of human patients.

REFERENCES