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Part 1: Dual-tuned proton/sodium magnetic resonance imaging of the lumbar spine in a rabbit model

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Abstract

Study Design—Development of a dual-tuned proton/sodium RF coil for magnetic resonance (MR) imaging of the rabbit spine and quantification of sodium concentration in intervertebral discs.

Objective—To develop the dual-tuned proton/sodium MR imaging of rabbit lumbar spine to investigate proteoglycan matrix content and intervertebral disc degeneration (IDD).

Summary of Background Data—IDD is a common chronic condition that may lead to back pain, limited activity, and disability. Early stage IDD involves the loss of proteoglycan matrix and water content in the disc. Sodium MR imaging is a promising noninvasive technique for quantitative measurement of proteoglycan changes associated with IDD. The combined structural (proton) and biochemical (sodium) MR imaging facilitates the investigation of morphological and molecular changes associated with degeneration of discs.

Methods—Multi-channel dual-tuned proton/sodium transceiver RF coil of the rabbit spine was developed and optimized at 3T human scanner – eight channels allocated for the sodium coil and four channels for the proton coil. High-resolution anatomy proton images of the discs were acquired using turbo spin echo and dual echo steady state sequence. Sodium concentration of the discs was quantified from sodium MR images that were calibrated for signal attenuation due to RF field inhomogeneity, sodium MR relaxation times, and disc thickness. Twelve rabbits (~1 year old, female, 5.2 ± 0.4 kg) were used for measuring disc sodium concentration.

Results—High-resolution in vivo proton and sodium MR images of rabbit discs (2-mm thickness) were successfully obtained using an in-house dual-tuned proton/sodium RF coil at 3T. The total acquisition time for each set of images was approximately 40 minutes. Sodium concentration of normal rabbit lumbar discs was measured 269.7 ± 6.3 mM, and this measurement was highly reproducible, with 5.3% of coefficient of variation.

Conclusion—Sodium concentrations of rabbit lumbar discs were reliably measured using our newly developed dual-tuned multi-channel proton/sodium RF coil at 3T.

Keywords

Dual-tuned proton/sodium MR imaging; Dual-tuned RF coil; Sodium concentration; Proteoglycan; Intervertebral disc degeneration

Introduction

Intervertebral disc degeneration (IDD) is a common chronic condition that may lead to back pain, limited activity, and disability¹. Early signs of IDD involve changes in the extracellular matrix composition of the nucleus pulposus (NP), which includes glycosaminoglycan (GAG) loss and the breakdown of proteoglycan (PG) aggregates². IDD inevitably results in loss of nucleus hydration and hydrostatic pressure and structural changes³. Development of effective treatments for IDD requires an understanding of the underlying pathogenesis and pathophysiology of the disease. Particularly, early non-invasive detection of IDD would be ideal for facilitating effective therapeutic intervention (e.g., biologic treatments) targeting modification of disease progression or preventive care^{4,5}. Efficacy of non-invasive techniques sensitive to early disc changes should be demonstrated on a suitable animal model. These techniques also require a demonstration of the stability and reproducibility of quantitative measurement of disc properties. This was the rationale for the development of the techniques described in this study.

Non-invasive magnetic resonance imaging (MRI) is commonly used to diagnose disc disease. MRI findings in disc are interpreted either qualitatively (e.g., image intensity)^{6–11} or quantitatively (e.g., morphology, MR physiology)^{12–16}. Changes in image intensity or morphology of the discs are frequently associated with advanced IDD¹⁷, but they may not be apparent with early IDD. Other MR characteristics, including T₂ relaxation time^{18,19}, diffusion^{12,14,20}, and T_{1ρ} relaxation time^{21–23}, were studied to diagnose early degenerative changes of the disc with limited success, because of the lack of the GAG specificity or the limitation of related MRI techniques. On the other hand, chemical exchange saturation transfer and diffusion tensor imaging are suggested as a potential biomarker to measure GAG changes²⁴ and annulus fibrosus (AF) integrity^{25,26}, respectively.

PG contains the highly negatively-charged GAG side chains which attract positive cations, primarily sodium ion (Na⁺)²⁷, hence sodium content (²³Na) is typically used as a surrogate marker to GAG^{18,28,29}. Previous papers^{27,29} showed a positive linear correlation between PG and sodium concentration [²³Na]. In addition, Wang et al.²⁷ demonstrated the feasibility of sodium MRI (²³Na-MRI) to diagnose the human IDD in vivo. Since PG loss is a universal hallmark of IDD (at early stage) and [²³Na] closely correlates with PG content, ²³Na-MRI can therefore potentially be used for the diagnosis of early stage IDD²⁷. However, ²³Na-MRI is technically more challenging than proton MRI (¹H-MRI) because of intrinsically low [²³Na] in tissue, low MR sensitivity, and fast T₂-signal decay (2 to 16 ms in normal human organs)^{27,30}. Multi-channel radiofrequency (RF) coil technique improves the signal-to-noise ratio because of its surface as well as volume coil characteristics^{31,32}. To facilitate the use of ²³Na-MRI for a useful IDD biomarker, it is preferable to perform additional high-resolution structural ¹H-MRI of the discs in a single session without repositioning of the subject. A dual-tuned (DT) RF coil serves this purpose as it allows the acquisition of both ¹H and ²³Na MR images in a single setting^{29,31,33}.

The rabbit model with annular-disc-puncture is well established as progressive IDD⁷, and the DT MRI is one of most suitable technologies to investigate the progressive pathophysiology changes and monitor the therapeutic effects at early stage. In this study, the purpose of this research is 1) to develop a DT MRI of the lumbar discs in a rabbit model in

vivo, 2) to test the performance of ^{23}Na -MRI, and 3) to quantify ^{23}Na in the normal discs using the new multi-transceiver DT RF coil at 3T.

Materials and Methods

All MRI was performed using a 3T human scanner (Siemens Medical Solutions, Germany).

RF coil and calibration phantom

A multi-channel DT coil was developed for $^1\text{H}/^{23}\text{Na}$ -MRI of the rabbit lumbar discs. The coil elements were constructed around two cylindrical plastic frames. Four-loops were wrapped around the outer ^1H coil frame (15-cm diameter, 16-cm length), and eight-loops were placed on the inner ^{23}Na coil frame (13-cm diameter, 12-cm length) (Supplemental Digital Content Fig. 1A); each coils were tuned to 123.2 and 32.58 MHz, respectively. Each coil loop was operated as an independent transceiver. Both coils were operated as a volume coil during transmission but as multi-channel surface coils during reception.

A homogenous phantom with a saline mixture of 36-mM ^{23}Na and 4% agar gel was used for the calibration of ^{23}Na MR images. Eight 50-cc syringes filled with 60-mM ^{23}Na in 4% agar gel were attached around the longitudinal center of the coil. These markers were used to co-register ^{23}Na images of the rabbits and the phantom (Supplemental Digital Content Figs. 1B–D).

Animal preparation

Twelve rabbits (New Zealand White, 5.2 ± 0.4 kg, from Myrtle's rabbitry) were used for the study approved by Institutional Animal Care and Use Committee. Prior to MRI, the animals were anesthetized with an intramuscular injection of ketamine (20 mg/kg), xylazine (5mg/kg), and acepromazine (1mg/kg). The rabbit was positioned supine at the coil center. Three rabbits were used to optimize MRI parameters. Twelve rabbits were scanned for $^1\text{H}/^{23}\text{Na}$ -MRI of lumbar discs. All rabbits underwent baseline scans, and six of them had two additional follow-up sessions at four and twelve weeks. Lumbar discs were harvested after sacrifice from one representative animal for histology analysis⁷. The discs were stained by Saffranin-O and examined under a light microscope (Nikon, Melville, NY) at 20 $\times$ magnification.

^1H and ^{23}Na -MRI

Same magnetic-field shim values were applied to both ^1H and ^{23}Na -MRI. ^1H images of the lumbar spine were acquired in sagittal view. T_2 -weighted turbo spin echo (TSE) image was acquired with repetition time (TR) = 3500 ms, echo time (TE) = 109 ms, resolution = $0.6 \times 0.6 \times 3$ mm³, and total acquisition time (TA) = 1:40 min. Dual echo steady state (DESS) imaging with fat suppression was also acquired with TR/TE = 14/5 ms, resolution = $0.6 \times 0.6 \times 3$ mm³, and TA = 1:04 min.

Following the ^1H -MRI, ^{23}Na -MRI was performed without re-positioning the animal. Three-dimensional (3D) ultra-short TE (UTE) spiral sequence³⁴ was applied with the following parameters; TR/TE = 60/0.27 ms, resolution = 2 mm³, readout time = 7.74 ms, and TA = 27 min. Hard RF pulse (500- μ s duration) was applied with 120–150 V, and the applied gradient slew-rate and maximum strength was 10 mT/mm and 10 mT/m, respectively. 3D image was reconstructed by re-gridding with a 3D Kaiser-Bessel convolution kernel ($4 \times 4 \times 4$)^{35,36} and fast Fourier transform. Hanning low-pass filter with bandwidth of 128 pixels was applied in k -space to reduce high-frequency noises.

^{23}Na MR image of the calibration phantom was also acquired using the same parameters as the rabbit imaging. The phantom image was used to correct B_1 -field inhomogeneity for the quantification of $[^{23}\text{Na}]$ of the discs.

Image processing and data analysis

Image processing was carried out using the customized Matlab program (MathWorks Inc., MA). In ^{23}Na MR images of the phantom and the rabbit, the reference markers were manually segmented and used to estimate the coordinate transform matrix between two images. Then, the matrix was applied to the rabbit images. The co-registered ^{23}Na MR image of rabbit spine was normalized using the phantom image to correct B_1 -field inhomogeneity and estimate the signal intensity with reference to the 36-mM $[^{23}\text{Na}]$ of the phantom. The RF power calibration in ^{23}Na image at different sessions was performed with reference to the mean intensity of the 60-mM $[^{23}\text{Na}]$ markers.

The signal reduction in $\sim 2\text{-mm}^3$ thin disc due to partial volume effect was simulated considering the applied filter and saline T_1 and T_2 , and compensated in measuring $[^{23}\text{Na}]$ of discs. The maximum intensity of ^{23}Na signals was projected in left-to-right (LR) and anterior-to-posterior (AP) direction in the manually selected region of interest (ROI) covering all lumbar discs. Residual ^{23}Na intensity variation in longitudinal (i.e., head-to-foot, HF) direction due to the coil characteristics was estimated by fitting ^{23}Na intensities measured from all normal lumbar discs using 3rd-order polynomial function. The nominal residual variation was inversely multiplied to the $[^{23}\text{Na}]$ profile in lumbar spine of each rabbit.

The variation in $[^{23}\text{Na}]$ measurements in discs was calculated by the percentage ratio of standard deviation (SD) and mean value. The reproducibility of $[^{23}\text{Na}]$ measurements between sessions was determined by means of the coefficient of variation (CV%).

Results

^1H anatomy and ^{23}Na -MRI of rabbit lumbar discs

High-resolution ^1H MR images of lumbar discs were achieved with clear demarcation of the discs from surrounding tissues and vertebral bodies (Figs. 1A and B). TSE image was highly contrasted in disc (water abundant) region (Fig. 1A). Hyperintensity region of TSE image was well coincided with NP in histology image (1st and 4th panels of Fig. 1D). DESS image showed high contrast in the discs but the disc shape was different from that in TSE image (Fig. 1B); the vertebral bone marrows were completely suppressed, whereas the ligament and AF regions remained visible (2nd and 4th panels of Fig. 1D). The discs in TSE image were thicker than those in DESS image (1st and 2nd panels of Fig. 1D). The high NP signal in TSE image and fat-suppressed intensity in DESS image could be used for the confirmation of structural damage in the discs.

Discs of normal rabbits in ^{23}Na images present with the brightest structure followed by the vessel and cerebrospinal fluid (Fig. 1C). However, the image intensities attenuated from the coil center to edge along the longitudinal direction (L1-2 and L6-S1 discs) (white arrow in Fig. 1C). This signal variation due to the B_1 -field inhomogeneity needed to be corrected for $[^{23}\text{Na}]$ quantification in discs. The discs in ^{23}Na image were thicker than those in ^1H images mainly due to low resolution and blurring artifact, but the intensity was highest in the NP (white arrowhead in 3rd panel of Fig. 1D). The signal attenuation due to the blurring in the disc from short T_2 and de-noising filtering were also compensated for $[^{23}\text{Na}]$ quantification.

Calibration for B₁ field and spatial filtering

MR images acquired with a surface-coil are typically present with a characteristic signal intensity gradient; high intensity in proximity of the coil that attenuates in depth from the coil (Supplemental Digital Content Fig. 1). B₁-field inhomogeneity estimated from the phantom image was used to correct ²³Na image of the rabbit spine (middle panel of Fig. 2A). Despite this correction of the global inhomogeneity, residual signal variation of ~25% was still noted from normal discs at L3-4 (coil center) to L1-2 (coil edge) (Fig. 2B). Thus, only the discs in the center region (±40 mm in HF) were considered for [²³Na] measurement. One-dimensional residual variation was corrected for the [²³Na] profile in HF axis (Fig. 2C).

Although a spatial filtering is necessary to remove high-frequency noises of ²³Na image, the filtering also affects the image intensity because the disc thickness (~2 mm) is smaller than the effective filter bandwidth (~4 mm) – the simulation results are presented in Supplemental Digital Content Fig. 2. In our analysis method, the noise distorted the projected ²³Na image intensity in the discs, particularly near the coil boundary – these artifacts could be removed by stronger filtering. However, ²³Na signal responded non-linearly to filter bandwidth the signal-drop with filter size 128 was not approximately two-fold lower than with filter size 60. The signal drop due to low-pass filtering and T₁ and T₂ decay was measured as ~23% from the original signal for 2-mm thick disc under the condition of filter bandwidth of 128, and T₁ and T₂ of 17.6 ms and 9.7 ms in the phantom (simulations in Supplemental Digital Content Fig 3). The signal-drop associated with the filtering and MR signal decay was compensated for [²³Na] measurement in the discs.

[²³Na] of rabbit lumbar discs

The mean [²³Na] of disc across the 6 lumbar discs was relatively constant 269.7 ± 6.3 mM, with the measurement variation of 6.3 ± 2.1 % (N = 12 rabbits) (left panel of Fig. 3). The mean [²³Na] of disc across the 12 rabbits was 265.7 ± 38.4 mM, with a greater measurement variation of 14.5 ± 2.8 % (N = 6 discs) (right panel of Fig. 3).

Reproducibility of ²³Na-MRI was tested over three different imaging sessions. The ²³Na-MRI within individual rabbits was highly reproducible (Fig. 4A). The mean [²³Na] of the lumbar discs at three different sessions were 267.5 ± 17.7 , 274.1 ± 24.32 , and 271.8 ± 20.1 mM (N = 6 rabbits): 7%, 9%, and 8% variation across the lumbar discs. Those were close to the measurement from the twelve rabbits at the baseline (Fig. 4B). Also, the mean [²³Na] of the lumbar discs acquired from six rabbits was reproduced for three sessions (Fig. 4C): 5.3% of CV%. The inter-rabbit [²³Na] variation from the six rabbits was 15%, 13%, and 13% for each session, which was close to the mean inter-rabbit variation from the twelve baseline rabbits.

Discussion

We successfully achieved anatomy ¹H-MRI of the rabbit lumbar discs at 0.6-mm resolution. The discs in TSE image with long TE appeared blurred due to local susceptibility between the vertebral bodies and the disc, whereas the blurring was not apparent in DESS image. Since long TE of TSE enhances the contrast between the discs and surrounding vertebral endplates, TE should be optimally selected to reduce the blurring while maintaining high T₂-contrast of the discs. Fat in the vertebrate body was effectively suppressed on the DESS image, whereas the signal of the longitudinal ligaments surrounding the discs persisted. This ligament signal may falsely increase the volume measurement of the disc. Therefore, the combined information of both TSE and DESS images will be helpful in determining the precise morphology of the discs. Besides of the anatomy MRI, other MR measurements

(e.g., T_2 or $T_{1\rho}$) can be simply added in the current MRI protocol. MR physiology changes associated with IDD was presented in the second part of this two-part series on the DT MRI (Part 2: Quantitative proton T_2 and sodium MR imaging to assess intervertebral disc degeneration in a rabbit model. *Spine* 2012; resubmitted).

The mean $[^{23}\text{Na}]$ of the rabbit lumbar discs was ~ 270 mM, which is within the range of previously reported disc $[^{23}\text{Na}]$ from different species (e.g., 150–300 mM in bovine disc²⁷). Since our $[^{23}\text{Na}]$ measurement in the rabbit discs was on the basis of local maxima of ^{23}Na distribution over the entire disc, our measurement is likely to represent that of NP. More systematic verification of the measurement is necessary using a phantom which simulates the rabbit discs with known $[^{23}\text{Na}]$. In addition, future study comparing $[^{23}\text{Na}]$ from MRI and disc PG content from quantitative biochemical assay is warranted to estimate PG loss associated with IDD.

The inter-rabbit variation of $[^{23}\text{Na}]$ in the discs was $\sim 15\%$, which is also similar to that of $[^{23}\text{Na}]$ in bovine $\sim 18\%$ [$= 50$ (SD) / 274 (mean)] (referenced from **Fig. 6A** in Wang et al.²⁷). However, the intra-rabbit variation across the discs was relatively small ($\sim 6\%$). This indicates the importance of an intra-rabbit comparison of $[^{23}\text{Na}]$ between normal and abnormal discs. Our in-vivo $[^{23}\text{Na}]$ measurement of the rabbit discs was highly reproducible and the average measurement variation was $\sim 1\%$ over three sessions. These results suggest that the quantitative measurement of $[^{23}\text{Na}]$ using MRI is useful for the longitudinal study of ^{23}Na and PG changes in the rabbit discs to investigate the underlying disease mechanism such as healing or degeneration process.

Direct B_1 -field mapping was not practical in our ^{23}Na -MRI of the rabbit discs within a reasonable acquisition time, because the rabbit discs are too small to yield sufficient ^{23}Na signal and no other neighboring structures except the disc to produce a detectable ^{23}Na signal at 3T. Thus, we estimated the B_1 field from a homogenous phantom image and the measured field inhomogeneity was corrected in ^{23}Na MR images of the rabbit discs, assuming similar B_1 field regardless of imaging objects at such a low ^{23}Na resonance frequency; the residual field variation was further corrected by polynomial fitting in longitudinal direction. However, for the accurate quantification of $[^{23}\text{Na}]$ in the discs further study of B_1 -field mapping and the correction method is necessary.

In conclusion, we successfully achieved high-resolution ^1H - and ^{23}Na -MRI of rabbit lumbar discs. We developed the reliable quantification method of $[^{23}\text{Na}]$ in the discs, and measured the $[^{23}\text{Na}]$ of normal rabbit lumbar discs using in-house DT $^1\text{H}/^{23}\text{Na}$ RF coil at 3T. This new imaging system should prove extremely useful for longitudinal investigation of IDD and testing the efficacy of different therapeutic interventions in the commonly used rabbit model of IDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Early signs of IDD involve changes in the composition of disc extracellular matrix, including reduced proteoglycan and conversion of collagen type II to type I.
- Proton MR imaging has the advantages of high signal and spatial resolution but its sensitivity for detecting changes in disc composition associated with early degeneration is limited. Conversely, sodium MR imaging is highly sensitive to changes associated with discs degeneration given a tight coupling between sodium and proteoglycan. Sodium MR imaging, however, is challenging because of low image resolution and intrinsically weak sodium MR signal, compared to proton imaging.
- In order to combine the strengths of proton and sodium MR imaging, we developed a new multi-channel dual-tuned RF coil adapted for the 3T human scanner. This novel dual-tuned proton/sodium MR imaging system is highly efficient for imaging of the rabbit spine and quantification of disc sodium content to assess IDD-related proteoglycan loss.

Fig. 1.

In vivo ^1H and ^{23}Na -MRI and histology of the rabbit spine discs. **A - B**, Sagittal image of the lumbar discs acquired by TSE and DESS ^1H -MRI, and UTE ^{23}Na -MRI all – images self-registered. Red and blue arrowhead represents blood vessel and cerebrospinal fluid, respectively. **D**, Comparison of different modality disc images – magnified in yellow rectangles in A to C. (Left to right panel) TSE, DESS, ^{23}Na , and histology images. Black arrows indicate anterior/posterior longitudinal ligament, and white arrowheads represent the disc nucleus pulposus. Abbreviation: L1–L6–lumbar vertebrates, S1–sacral vertebrate, H–head and A–anterior. NP–nucleus pulposus, AF–annulus fibrosus. Same abbreviations were applied to following figures.

Fig. 2.

Quantitative ^{23}Na -MRI of the rabbit lumbar discs. **A**, (Left panel) T_2 -weighted TSE ^1H image, (Middle panel) ^{23}Na MR image after B_1 -field correction, and (Right panel) fusion of the TSE ^1H and ^{23}Na images in sagittal view. **B**, Residual B_1 -field inhomogeneity in ^{23}Na image in head-to-foot direction ($N = 12$ rabbits). **C**, Corrected [^{23}Na] profile of a rabbit lumbar spine (following the black dotted curve in the middle panel in A).

Fig. 3. ^{23}Na of rabbit lumbar discs. (Left panel) Mean ^{23}Na of discs across the 6 lumbar discs (N = 12 rabbits). (Right panel) Mean ^{23}Na of 6 lumbar discs in 12 different rabbits. Note that the inter-rabbit variation in ^{23}Na of discs was greater than the inter-disc variation.

Fig. 4. Reproducibility of [^{23}Na] measurement. **A**, ^1H and ^{23}Na MR images (left and right panel, respectively) at three sessions of baseline (session 1), 4 weeks (session 2), and 12 weeks (session 3), respectively. White-dotted line represents L6-S1 disc position. **B**, Mean [^{23}Na] of discs (N = 6 rabbits) at different disc levels across three sessions. **C**, Mean [^{23}Na] of discs (N = 6 discs) in different rabbits across three sessions.