Functional Consequences of Aquaporin-1 Deficiency: Renal MRI in a Pre-clinical Model

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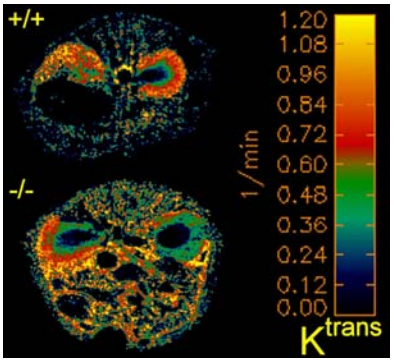
Introduction. Aquaporins are a family of membrane proteins that are selectively permeable to water. The aquaporin-1 (AQP1) water channel is widely expressed in fluid-transporting epithelia and endothelia, particularly in the kidneys. Transgenic knockout mice deficient in AQP1 have been found to be polyuric and unable to concentrate their urine in response to water deprivation[1]. We have employed Dynamic Contrast-enhanced MRI (DCE-MRI) and Blood Oxygen-Level Dependent (BOLD) MRI to quantify alterations in filtrate pH and medullary workload, and compensatory changes in glomerular filtration rates, in AQP1-knockout (AQP1ko) mice.

Methods. MRI was performed on a Bruker Biospec 4.7 T system with 20 G/cm self-shielded gradients, using a 25 mm Litz coil. Mice were anesthetized by inhaled isoflurane (1.5%, rest O_2 at 1 L/min), and circulating warm water jackets were used to keep animals warm in the magnet. Mouse body temperature was monitored during all MRI experiments using a rectal fluoroptic temperature probe (Luxtron Corporation, Santa Clara, CA, USA). Mice were cannulated at the tail vein prior to positioning in the magnet, and contrast agent (0.015-0.025 mmole/Kg) and saline chase (0.12 mL) were administered via this catheter at the appropriate time during each experiment. All images were acquired using a fat-suppressed radial spin-echo sequence. Pre-contrast T_1 maps were calculated from images acquired prior to administration of contrast agent with the following parameters: TR = 3.0, 0.5 and 0.1 s, TE = 9 ms, no. of radial lines = 256. During the dynamic portion of the imaging experiment, radial lines were collected repetitively with the above parameters and TR = 0.1 s for 30 minutes, with Gd-DOTP (Macrocyclics Inc., Dallas, TX) & saline chase being injected over 30 seconds 8.5 minutes after start of imaging. The dynamic portion of the experiment was then repeated using Gd-DOTA-4AmP (Macrocyclics Inc.). Images were reconstructed offline via filtered back-projection using a sliding window moving 64 lines per image, yielding an effective temporal resolution of 6.4 s. A "vascular normalization function"[2] was obtained for each injection from pixels which enhanced at least 3-fold and reached maximum enhancement within 60 seconds after start of injection. The pharmacokinetics of signal enhancement following the Gd-DOTP bolus were fitted to the extended Tofts model[3]. The model yielded 3 fitted parameters: K^{trans}, related to the volumetric filtration rate (mL/min per mL tissue), v_e, the extracellular extravascular volume fraction (dimensionless), and v_p, the plasma volume fraction (dimensionless). pH was computed from the pharmacokinetics of Gd-DOTP & Gd-DOTA-4AmP as per the method of Raghunand et al.[4]. Co-registered T2* maps were calculated from gradient-echo images collected with the following parameters: TR = 300 ms, TE = 5, 10, 15,.., 40 ms (8 images), 256x256 matrix, flip angle $\alpha = 45°$.

Results & Conclusions. Calculated maps of K^{trans} from a control mouse and an AQP1ko mouse are shown in the figure below. The cross-section of the right kidney in the control mouse (top) clearly shows a high volumetric filtration rate in the cortex, somewhat lower values in the medulla, and very low values in the renal pelvis, as expected. The left kidney in the AQP1ko mouse (bottom) displays nearly normal volumetric filtration rates, except for a region of apparently absent function at the dorsal face. The right kidney in AQP1ko mice exhibited a marked decrease in filtration function, as evident here, and this was found to correlate to hydronephrosis. Other measured parameters are listed below:



Parameter	Control Mice	AQP1-knockout Mice
K^{trans} (min^{-1}), Renal Cortex	0.9 ± 0.13 (n=3)	0.6 ± 0.3 (n=3)
v_e (dimensionless), Renal Cortex	0.3 ± 0.08 (n=3)	0.08 ± 0.04 (n=3)
pH, Renal Cortex	6.9 ± 0.3 (n=3)	6.6 ± 0.4 (n=3)
T_2* (ms), Renal Medulla	42 ± 6 ms (n=7)	23 ± 11 ms (n=3)

The hydronephrosis that was evident in all AQP1ko mice is reflected in the low apparent values of cortical v_e. The lower volumetric filtration rates (K^{trans}) in the AQP1ko mice is also evident. This decrease in filtration function is possibly mediated via tubuloglomerular feedback as a compensatory response to the threat of NaCl depletion caused by defective proximal tubule reabsorption, or may be a consequence of the hydronephrosis itself. A more acidic renal pH in AQP1ko mice, relative to wild-type mice, was measured. A possible explanation is provided by the recent report of increased expression of vacuolar-type H^+-ATPase in the inner medullary collecting duct of AQP1ko mice[5]. Medullary T_2* was lower in AQP1-ko mice relative to control mice, indicating decreased medullary pO_2. Worsening of medullary hypoxia may be a consequence of increased work load to recover ions being lost through increased urine production in the AQP1-knockout mice. Alternately, the lower T_2* may be a reflection of an increase in blood volume fraction. It has been reported that the diameter of the outer medullary descending vasa recta (OMDVR) in AQP1-knockout mice is 1.9-fold the diameter of the OMDVR in wild-type mice[6]. DCE-MRI and BOLD MRI can thus provide unique and valuable insights into the role of Aquaporin-1 in renal function that cannot be obtained by more traditional invasive techniques.

References:

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