$H_2{}^{17}O$ as a "smart" T_2 contrast agent with relaxivity sensitive to tissue metabolic status

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Introduction

There are a broad range of MR methods to monitor tissue metabolic status, relying on intrinsic contrast mechanisms (T_1 and T_2 weighted imaging), tissue biophysical properties (diffusion imaging), or the introduction of exogenous agents (contrast agents, isotopic labels). We present a novel method to monitor perturbed metabolic status via a T_2 contrast agent with relaxivity modulated by tissue pH and phosphate concentration.

Scalar coupling interactions between ^{17}O and covalently bonded protons reduce the T_2 of protons in $H_2{}^{17}O$ (1). In an aqueous solution containing $H_2{}^{17}O$ this T_2 relaxivity effect is transmitted to bulk water protons by proton exchange, and a relatively small ^{17}O enrichment of water can have a large effect on water proton T_2. The relaxivity effect is minimal when water exchange is in the fast regime, and maximal at intermediate exchange rates. Water proton exchange rate is pH sensitive. We have previously demonstrated that exchange rate measurements can be used to measure sample pH in *in vitro* studies (2). However as the T_2 relaxivity of $H_2{}^{17}O$ is affected by any reaction that can alter water proton exchange rate, the presence of metabolites capable of catalyzing water proton exchange (such as phosphate) can alter the calibration between tissue pH and $H_2{}^{17}O$ T_2 relaxivity. Thus measurements of proton exchange rate cannot be used as a direct measurement of pH in all tissues. In this study we examined the ability to distinguish between normal and ischemic brain tissue via water proton exchange rate, distinguishing between tissue with near-neutral pH and low phosphate content (normal) and tissue with acidic pH and elevated phosphate content (ischemic). We thus employed $H_2{}^{17}O$ as a "smart" T_2 contrast agent with relaxivity dependent on tissue metabolic status. We administered $H_2{}^{17}O$ to mice to elevate the ^{17}O enrichment of body water to ~1.5%, then compared the T_2 of brain water protons under normal *in vivo* and *post mortem* conditions.

Figure 1 shows plots of the T_2 relaxivity of $H_2{}^{17}O$ for sample pH between 5 and 9, at 1, 5 and 10 mM phosphate concentrations. At low phosphate concentrations the T_2 relaxivity of $H_2{}^{17}O$ is approximately constant over the physiological pH range. Increased phosphate content clearly decreases the T_2 relaxivity.

Methods

Female CD1 mice were administered 70% ^{17}O-enriched water (16 g/kg body weight) to produce an approximately 1.5% ^{17}O enrichment of body water (assuming a body water content of ~70%). Labelled water equilibrated with body water for two hours prior to MR imaging. Animals were anesthetized with isoflurane (2% in O_2), placed in a cradle and a home-built quadrature surface coil placed over the head. Respiration, heart rate and body temperature were monitored for the duration of the experiments. MR data were acquired on a 4.7 T, 30cm diameter horizontal bore magnet and spectrometer. After acquisition of localizer scans a multi-slice multi-echo sequence (TE = 20 ms, 10 echoes per repetition, TR = 3000 ms) and diffusion-weighted spin echo sequences (b = 150 and 1500, δ = 6, Δ = 20, TE = 36, TR = 2300) were acquired. Global hypoxia was initiated by exchanging the anesthetic carrier gas with nitrogen. Image acquisition was repeated after failure of heart function. T_2 and ADC maps were generated from the MR datasets using in-house software written in Matlab (The MathWorks, Natick MA, USA).

Results

Figure 2 shows T_2 maps generated from multi-slice multi-echo images acquired from a control mouse (no $H_2{}^{17}O$). *Post mortem* T_2 values show little change from *in vivo* values, with a mean T_2 of 61 and 61 ms for *in vivo* and *post mortem* brain respectively. Elevated signal was observed in diffusion weighted images acquired from *post mortem* brain compared to *in vivo* brain (data not shown), confirming onset of hypoxia. Figure 3 shows T_2 maps from a mouse administered $H_2{}^{17}O$ to a body water enrichment of ~1.5%. *In vivo* T_2 values are approximately 15-20% lower than in control mice due to the presence of $H_2{}^{17}O$, mean brain T_2 was 52 ms. *Post mortem* T_2 values were elevated compared to *in vivo* values with a mean T_2 of 57 ms. The change in T_2 between *in vivo* and *post mortem* brain is assigned to a decrease in $H_2{}^{17}O$ relaxivity, resulting from an increase in water proton exchange rate caused by a change in tissue pH and phosphate content.

Discussion and Conclusions

$H_2{}^{17}O$ administration to mice caused a decrease in brain water proton T_2. As the extent of $H_2{}^{17}O$'s relaxivity effect is dependent on the water proton exchange rate, which is in turn dependent on tissue pH and phosphate content, the T_2 relaxivity of $H_2{}^{17}O$ was higher in normal tissue than in ischemic tissue. Thus $H_2{}^{17}O$ can act as a "smart" contrast agent with relaxivity sensitive to tissue metabolic status. Furthermore, as the exogenous contrast agent is isotopically labeled water, the method is as minimally invasive as is possible. Other methods and contrast agents could be applied to measurement of exchange rates in tissues, providing alternative methods of detecting changes in metabolic status. For example, CEST contrast agents have been proposed for pH-sensitive contrast (3). Zhou *et al*. have measured changes in brain tissue pH (REF) via amide proton transfer rates, however the magnitude of the signal change in their measurements was small compared to those reported here, and our data suggest that metabolites capable of catalyzing proton exchange (in our studies, phosphate) may disrupt calibrations of exchange rate versus pH. Studies measuring the concentration of $H_2{}^{17}O$ via its T_2 relaxivity effect must consider the effect of changing proton exchange rate in the interpretation of their results, as our data show that the T_2 relaxivity effect of $H_2{}^{17}O$ is dependent on pH and phosphate content, as well as $H_2{}^{17}O$ concentration.

References and Acknowledgements

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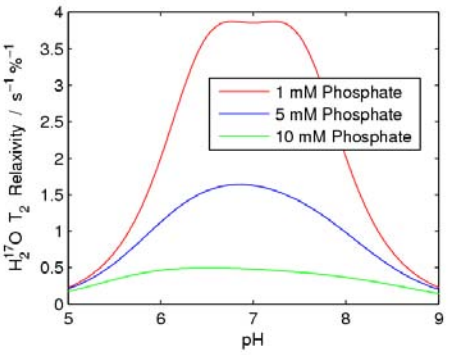

Figure 1 (Left)
Plot of the T_2 relaxivity effect of $H_2{}^{17}O$ on water protons at sample pH between 5 and 9, calculated for phosphate concentrations of 1, 5 and 10 mM

Figure 2 (Right)
T_2 maps of mouse brain water protons in control (A, B) and $H_2{}^{17}O$-enriched (C, D) under normal *in vivo* conditions (A, C) and during global ischemia (B, D). Water proton T_2 values are shorter in $H_2{}^{17}O$ enriched mice, and $H_2{}^{17}O$ relaxivity is greater in normoxic conditions than following ischemia.