Natural D-glucose as a biodegradable T_2 contrast agent for MRI

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TARGET AUDIENCE: Investigators interested in exogenous MRI contrast agents suitable for human translation.

PURPOSE: Chemical exchange of protons between solute molecules and the bulk water can affect the transverse relaxation rate ($R_2 = 1/T_2$) of the large bulk water resonance. The relaxivity due to chemical exchange (R_{2exch}) is dependent on factors such as the exchange rate of the solute protons to water (k_{sw}) and the chemical shift difference between the exchanging sites ($\Delta\omega_{II}$) At higher magnetic field strengths, $\Delta\omega_{II}$ increases causing R_{2exch} to be field dependent. Previously, exogenous paramagnetic contrast agents with large chemical shift differences have exploited this phenomenon to selectively alter the bulk water R_2 for MRI contrast.[1,2] Here we show that simple natural D-glucose, with its 5 exchangeable hydroxyl protons, is an excellent T_2 contrast agent that is ideally suited for use under physiological conditions at human MRI field strengths.

METHODS: D-glucose was dissolved in phosphate buffered saline (PBS) at concentrations of 1, 3, 5, 10, 20 mM and the pH adjusted to 7.3. In addition, a group of 10 mM solutions was prepared with pH values of 6.3, 6.8, 7.8, and 8.3. These solutions were placed in separate 5 mm NMR tubes and imaged at 3 and 7 T on human MRI scanners (Philips Healthcare). T_2 measurements were made on these solutions using a Carr-Purcell-Meiboom-Gill (CPMG) preparation period followed by a single-shot fast spin-echo imaging (FSE) readout. τ_{CMPG} was fixed at 20 ms whilst the number of pulses was varied between 4-24. The pre-scan delay before each preparation period was 15 s (>5 x T_1). To check for changes in viscosity with increasing glucose concentration, which can also affect transverse relaxivity, the apparent translational diffusion coefficient was measured using a DWI sequence.

RESULTS: The apparent diffusion coefficients (D) for the glucose solutions were independent of concentration (for 1-20 mM range) and pH (Fig. 1a). From Figs. 1b,c, we can clearly see a strong concentration, pH, and magnetic field strength dependence for the water transverse relaxation rate constants ($R_2 = 1/T_2$) of the glucose solutions. For this low concentration (mM) range, the concentration dependence in Fig. 1b is approximately linear, which allowed us to fit out R_{2exch} ($R_2 = R_{2water} + [glucose]R_{2exch}$). For 10 mM solution, R_{2exch} = 20.8 $s^{-1}mM^{-1}$ at 3 T and R_{2exch} = 60.2 $s^{-1}mM^{-1}$ at 7 T. In Figure 1c, the largest relaxivity is observed at physiological pH (7.3).

DISCUSSION: Minimal changes in D as a function of concentration indicate that the concentrations used here did not affect the viscosity of the solutions. Consequently, we conclude that changes in relaxation with concentration are due to the exchangeable hydroxyl protons in glucose. R_{2exch} per mM of glucose is much higher at 7 T compared to 3 T which shows that glucose would be a better contrast agent at higher magnetic field strength. Also, from Fig. 1c, we can conclude that the greatest effect of this transverse relaxivity agent happens to be in the physiological pH range.

CONCLUSIONS: The relaxation properties of D-glucose shown in this study indicate that it is well suited as an exogenous T_2 contrast agent for MRI under physiological conditions. The five exchangeable hydroxyl protons of glucose are able to cause measurable changes in transverse relaxation of water, even at relatively low concentrations of 10 mM, already allowed for human use. In addition, the largest changes in relaxivity are observed in the physiological pH range, which is promising for in vivo applications. This adds another application for the use of glucose, which was recently found also to be suitable to image glucose uptake in tumors.[3,4] The principles outlined here can be extended to other biodegradable agents containing exchangeable protons.

REFERENCES: 1. Aime, et al., Invest Radiol 1988:23:S267. 2. Soesbe et al., Magn Reson Med 2011:66:1697. 3. Chan et al. Magn Reson Med 2012, available on-line. 3. Walker-Samuel, et al. In Proceed. 20th ISMRM, 2012. p. 182. Grant support: NIH/NIBIB: R01EB015032

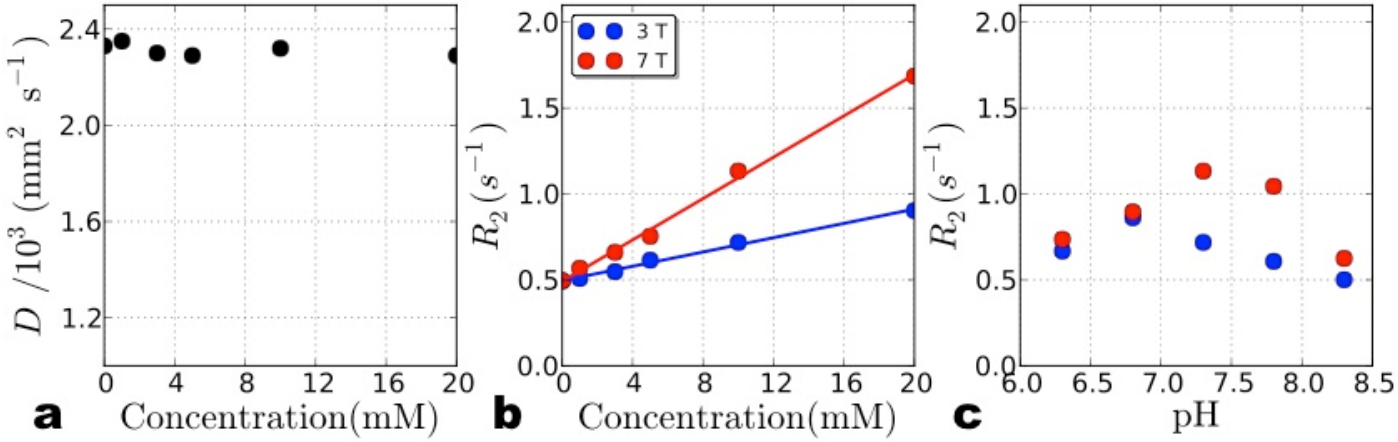

Figure 1 (a) Apparent translational diffusion coefficient at room temperature measured for different concentrations of glucose. Concentration (b) and pH (c) dependence of transverse relaxivity for D-glucose solutions at 3 T and 7 T. Solutions at different concentrations were adjusted to pH 7.3 (b), while solutions at different pH had a D-glucose concentration of 10 mM (c).