Heteronuclear relaxivity of commercial gadolinium contrast agents

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Introduction

Recent applications of dynamic nuclear polarization (DNP)[(1)] have led to increasing interest in non-proton MR for metabolic and molecular imaging. Nuclei with long relaxation times are needed to effectively use the high non-equilibrium hyperpolarization attained by these techniques. However, performing thermal equilibrium experiments of nuclei with long T_1 is problematic and time consuming. Paramagnetic contrast agents can be employed to shorten T_1 of nuclei other than proton [(2)]. The relaxivities of two commercial gadolinium contrast agents on the heteronuclear relaxation of ^{13}C and ^{15}N are reported. Significant differences are observed between Magnevist and Omniscan due to electrostatic effects and are broadly in agreement with an outer sphere relaxation mechanism, previously observed also by ^{1}H NMR[(3)]. The effect of contrast agents has also been examined in cell suspensions, as monitored by ^{31}P NMR, and found to exert little influence on the relaxation properties of intracellular phosphocholine.

Methods and Results

NMR experiments were conducted on a Bruker Avance 500MHz spectrometer (Bruker Instruments, Germany). The relaxation times of the two carbons in ^{13}C labeled glycine and the ^{15}N in labeled choline (84% H_2O/16% D_2O) were measured using a standard inversion recovery sequence. The relaxivity r_1 was measured from the linear fit of the plot $R_1 = 1/T_1$ as a function of contrast agent concentration (mM). Gadolinium contrast agents $[Gd\text{-}(DTPA)(H_2O)]^{2-}$ (Magnevist, Schering) and $[Gd\text{-}(DTPA\text{-}BMA)(H_2O)]$ (Omniscan, Amersham Healthcare) were used as supplied for clinical use. The paramagnetic contrast agents were added into glycine and choline solutions and into cell suspension in concentration ranging from 0.1 to 1 mM, corresponding to 1 to 10 fold the clinical dose (200 µl/kg).

Human MDA-MD-231 breast cancer cells ($80\cdot10^6$) were grown at 37° C in DMEM, harvested by trypsinization, washed in phosphate buffered saline (PBS) and centrifuged to form a pellet. The pellet was resuspended in PBS and placed in a NMR tube with a susceptibility plug at the bottom to prevent the cells sedimenting below the coil sensitivity region. ^{31}P NMR spectra of the cell suspension were acquired at 202.45 MHz using a 30 degree pulse-and-acquire sequence with proton decoupling, ns=128, at T=25° C temperature.

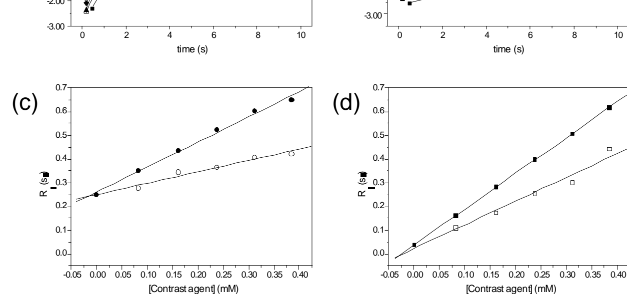

Fig. 1 Inversion recovery curve for (a) ^{13}C **α** and (b) ^{13}CO in ^{13}C labeled glycine in water/16%D_2O at the concentrations of Magnevist reported in figures (c) and (d) respectively. (c-d) Corresponding linear fit of $R_1 = 1/T_1$ to calculate the relaxivities for Omniscan (○) and Magnevist (■).

In Fig. 1 the inversion recovery curves of ^{13}C glycine Cα and CO are reported at different concentrations of Magnevist, along with the linear fit to calculate the relaxivity of Magnevist and Omniscan. Similar results (not shown) were found for ^{15}N in choline. In Table 1 the measured relaxivities at 11.7T are reported.

In Fig. 2 ^{1}H and ^{31}P spectra of a cell suspension with 0 and 1 mM Omniscan are shown. Below in Fig. 2C the linewidth of extracellular water peak and intracellular phosphocholine (PCho) are reported. While Omniscan has a marked effect on the extracellular water peak, intracellular PCho is not noticeably affected by the extracellular presence of the Gd-contrast agent.

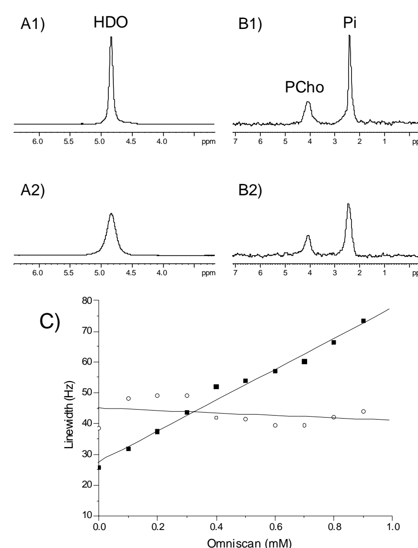

Fig. 2 ^{1}H (A) and ^{31}P (B) spectra of HDO peak in a cell suspension in PBS solution with no (A1-B1) and 1mM (A2-B2) Omniscan. PCho is intracellular while Pi is both intra- and extracellular. C) Linewidth of extracellular HDO (■) (^{1}H) peak and intracellular PCho (○) (^{31}P) as a function of Omniscan concentration.

	^{13}C α Gly	^{13}C CO Gly	^{15}N choline	^{1}H HDO
Omniscan	0.48±0.04	1.0±0.08	0.043±0.001	4.68±0.01
Magnevist	1.1±0.04	1.5±0.04	0.124±0.002	4.16±0.01

Table 1: Relaxivities (mM^{-1} s^{-1}) at 11.7T of ^{13}C in glycine, ^{15}N in choline, and ^{1}H HDO peak for Magnevist and Omniscan in aqueous solution.

Conclusion

We have presented relaxivities of two commercial contrast agents on ^{13}C and ^{15}N on two metabolites with long intrinsic relaxation times. Relaxivities are lower compared to proton; however a significant change in the relaxation time of ^{13}C and ^{15}N can be achieved with a few µM of contrast agent. Addition of 0.1mM Magnevist reduces the intrinsic ^{15}N T_1 in choline of 285s to 64s. Extracellular gadolinium contrast agents do not show significant susceptibility effect on the intracellular metabolite PCho. This presumably would also show no effect on the relaxation time of intracellular metabolites and be important in the future use of hyperpolarized tracers to wash out the extracellular parent signal and better observe the intracellular daughter compounds.

Acknowledgements

This work was supported by Cancer Research UK [CUK] grant number C1060/A5117 and by the Council for Research Councils Basic Technology Programme grant number GR/S23612/01.

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