Published in final edited form as:

Phys Med Biol. 2003 November 7; 48(21): N277–N282.

A quantitative study of magnetization transfer in MAGIC gels

Daniel F Gochberg¹, Peter M Fong², and John C Gore¹

Daniel F Gochberg: daniel.gochberg@vanderbilt.edu

¹Department of Radiology and Radiological Sciences, Vanderbilt Medical School, Institute of Imaging Science, Vanderbilt University, 1161 21st Avenue S, R-1302 MCN, Nashville TN 37232-2675, USA

²Department of Biomedical Engineering, Yale University, PO Box 208284, New Haven, CT 06520-8284, USA

Abstract

Magnetization transfer (MT) has been measured quantitatively as a function of radiation dose in MAGIC polymer gels. The MT rates between the free and immobile macromolecular proton pools (k_{mf} and k_{fm}), and the ratio of the sizes of these coupled proton pools (p_m/p_f), were measured by analysing the response to an inversion recovery sequence. While p_m/p_f increases linearly with dose, the fast MT rate k_{mf} also increases with dose, unlike previous measurements in BANG gels. This dependence of k_{mf} on dose suggests there are additional factors that modify spin exchange in MAGIC gels as irradiation occurs.

1. Introduction

The potential for using MRI to measure radiation dose distributions was first demonstrated (Gore *et al* 1984) using the radiation response of the Fricke ferrous sulphate dosimeter. More recently, polymer gels (in which radiation-induced polymerization alters water relaxation times) have been developed and provide more localized effects in comparison to Fricke gels in which ions diffuse freely. A variety of such gels has been formulated based on acrylamide or acrylic acid and *N,N'*-methylene-bisacrylamide (BIS) (Maryanski *et al* 1994, 1996). A new dosimetry gel called MAGIC (Fong *et al* 2001) has the great advantage of responding well when prepared in a normal atmosphere. This paper reports our measurements of the parameters that describe magnetization transfer (MT) in such gels. Knowledge of the MT parameter values as a function of dose may help to elucidate the processes which occur during irradiation and guide imaging methods for mapping dose distributions based on MT (Lepage *et al* 2002) (rather than the more common T_2).

In previous relaxation studies of acrylic polymers (Kennan *et al* 1996, Gochberg *et al* 1998), we reported the effects of different surface groups, pH, and the degree of cross-linking on the efficacy of MT. A second study (Gochberg *et al* 2001) measured relaxation and MT in acrylamide and acrylic acid polymer gels. Here, we report the results of quantitative measurements of MT in MAGIC gels in which the degree of radiation-induced polymerization is varied.

The gels are considered to comprise two main proton pools that exchange magnetization and vary in size as polymerization proceeds. The two pools comprise the free, mobile solvent protons whose resonance is motionally narrowed and a second proton pool corresponding to macromolecular protons that are relatively immobile and hence show broad resonances.

2. Methods and materials

The longitudinal relaxation rate, R_1 , the rates of MT from the macromolecular proton pool to the free solvent proton pool (k_{mf}) and in the reverse direction (k_{fm}), and the ratio of the size of the macromolecular proton pool to the free solvent proton pool (p_m/p_f) were measured for a series of gels irradiated with doses between 0 and 54 Gy at a dose rate of 1.76 Gy min⁻¹. The MT parameters were measured using a selective inversion recovery imaging experiment (Edzes and Samulski 1978, Gochberg *et al* 1997, Gochberg and Gore 2003). The details of the experimental NMR procedures are explained elsewhere (Gochberg and Gore 2003) and only a brief synopsis will be given here.

We employ a modified inversion recovery sequence followed by echo planar imaging. The inversion pulse is designed to selectively invert the free solvent proton pool while minimally disturbing the macromolecular pool. The evolution of the free water proton signal following the inversion (when there is no applied radio frequency radiation) is then given by Edzes and Samulski (1977, 1978):

$$\frac{M_f(t)}{M_{f\infty}} = b_f^+ \exp(-R_1^+ t) + b_f^- \exp(-R_1^- t) + 1 \quad (1)$$

where

$$2R_1^\pm = R_{1f} + R_{1m} + k_{fm} + k_{mf} \pm \sqrt{(R_{1f} - R_{1m} + k_{fm} - k_{mf})^2 + 4k_{fm}k_{mf}} \quad (2)$$

$$b_f^\pm = \pm \frac{\left[\frac{M_f(0) - M_{f\infty}}{M_{f\infty}} \right] (R_{1f} - R_1^\mp) + \left[\frac{M_f(0)}{M_{f\infty}} - \frac{M_m(0)}{M_{m\infty}} \right] k_{fm}}{R_1^+ - R_1^-}. \quad (3)$$

R_1^- is the slow recovery rate, which is often referred to as the measured value of R_1 . R_1^+ is a fast recovery rate. The subscripts f and m refer to the free solvent and macromolecular (immobile) proton pools, respectively. $M_f(t)$ is the longitudinal magnetization of the mobile protons at time t , whose equilibrium value is $M_{f\infty}$. R_{1f} and R_{1m} are the longitudinal relaxation rates of the mobile and macromolecular protons when there is no magnetization transfer between them.

For the case of k_{mf} much greater than all other terms in equation (2), as is commonly found in macromolecular structures and will be assumed in our analysis, $R_1^+ \approx k_{mf}$ and

$$b_f^+ = \left(\frac{M_f(0)}{M_{f\infty}} - \frac{M_m(0)}{M_{m\infty}} \right) \frac{p_m}{p_f} \quad (4)$$

allowing a determination of the rate of MT (k_{mf}) and the pool size ratio (p_m/p_f) by measurements of R_1^+ , b_f^+ , and $M_f(0)/M_{f\infty}$ and numerical simulations of $M_m(0)/M_{m\infty}$ (assuming a rough estimate of T_{2m} and a repetition time much longer than $1/R_{1m}$). k_{fm} can then be determined by simple multiplication: $k_{fm} = k_{mf} p_m/p_f$.

All measurements were made using a 2 T spectrometer with a Bruker Avance console, using a bird cage coil. Images of seven samples exposed to varying dose levels were imaged concurrently. The response of the signal from the mobile proton pool was then analysed in terms of two compartments coupled by exchange.

Data fitting was performed on central regions of each sample, and uncertainties were determined by 95% confidence level as determined by Matlab's Gauss–Newton non-linear fitting procedure and a Jacobian and residual-based analysis. Such an error analysis ignores variations in the samples that may cause correlations in the variations of the parameters.

The composition and manufacturer of the materials used were 300 bloom gelatin from Aldrich (8% w/w); 27,160-8, Mallinkrodt Ascorbic Acid 1852-10 (2×10^{-3} M), Aldrich CuSO₄, 20,919-8 (8×10^{-5} M), Sigma Methacrylic Acid M0782 (9 % w/w), HPLC grade distilled water and Sigma hydroquinone H-7148 (1.8×10^{-2} M).

3. Results

Figures 1–4 are calculated plots of R_1 , p_m/p_f , k_{mf} and k_{fm} , respectively, as a function of radiation dose. Least squares linear fits to the data between 0 and 16 Gy give results as follows: $p_m/p_f = 0.031 \pm 0.002 + \text{dose} \times (0.0017 \pm 0.002 \text{ Gy}^{-1})$; $k_{mf} = 50 \pm 5 \text{ Hz} + \text{dose} \times (3.6 \pm 0.5 \text{ Hz Gy}^{-1})$; $k_{fm} = 1.4 \pm 0.3 \text{ Hz} + \text{dose} \times (0.29 \pm 0.03 \text{ Hz Gy}^{-1})$. The choice of 16 Gy as the endpoint of the linear region was made by visual inspection.

4. Discussion

Figures 1 and 2 illustrate the expected relationship between R_1 and the pool size ratio versus irradiation dose: a roughly linear increase at first that then curves into a plateau. (An exponential approach to equilibrium may be a more accurate description (Lepage *et al* 2001)). Surprisingly, figure 3 shows a similar pattern for k_{mf} . This result is in stark contrast to previous measurements in BANG and BANG 2 gels (Gochberg *et al* 2001), where k_{mf} was found to be independent of dose. The current results do not, however, affect the seemingly linear dependence of k_{fm} versus dose, as illustrated in figure 4.

Since $k_{fm} = (p_m/p_f) \times k_{mf}$, all three parameters cannot be, in an exact mathematical sense, linear versus dose concurrently, e.g., if $p_m/p_f = c_1 \text{ dose} + c_2$ and $k_{mf} = c_3 \text{ dose} + c_4$, then k_{fm} would have a non-linear $c_1 c_3 \text{ dose}^2$ term. However, least squares linear fits for the data points between 0 and 16 Gy give goodness-of-fit Q values (as calculated in Press *et al* 1992) of 0.962, 0.987 and 0.998 for p_m/p_f , k_m and k_{fm} , respectively. These values are well above the 0.1 required for being a good fit to the model, indicating that a linear fit is an adequate model at this signal-to-noise level.

The linear dependence of k_{mf} indicates that the mechanisms involved in spin transfer from the macromolecular proton pool to the free water pool change with dose. This effect is as yet unexplained, though possibilities include dose dependence of the pH, macromolecular association constants and/or macromolecular morphology. MT parameters have been shown to be dependent on pH (Gochberg *et al* 1998) and association constants may be influenced by long-range electrostatic effects (Tanford 1961), while morphologic changes may alter access of free solvent to spin exchanging sites. A further possibility is that the monomer methacrylic acid grafts to gelatin with irradiation. The number of conduits for MT between the gelatin and the solvent might then increase with dose. Clearly, however, the behaviour of MT within MAGIC gels differs in some fundamental manner from MT within BANG co-monomers, and understanding these differences may provide new opportunities for designing improved gels for dosimetry.

Acknowledgments

The authors would like to thank Martin Lepage for helpful discussions concerning gel dosimetry and Jeff Luci for preparation of gels. This work was supported by grant CA 090844 and EB00214-14.

References

- Edzes HT, Samulski ET. Cross relaxation and spin diffusion in the proton NMR of hydrated collagen. *Nature*. 1977; 265:521–523. [PubMed: 834303]
- Edzes HT, Samulski ET. The measurement of cross-relaxation effects in the proton NMR spin-lattice relaxation of water in biological systems: hydrated collagen and muscle. *J. Magn. Reson.* 1978; 31:207–229.
- Fong PM, et al. Polymer gels for magnetic resonance imaging of radiation dose distributions at normal room atmosphere. *Phys. Med. Biol.* 2001; 46:3105–3113. [PubMed: 11768494]
- Gochberg DF, Gore JC. Quantitative imaging of magnetization transfer using an inversion recovery sequence. *Magn. Reson. Med.* 2003; 49:501–505. [PubMed: 12594753]
- Gochberg DF, et al. Quantitative studies of magnetization transfer by selective excitation and T1 recovery. *Magn. Reson. Med.* 1997; 38:224–231. [PubMed: 9256101]
- Gochberg DF, et al. The role of specific side groups and pH in magnetization transfer in polymer gels. *J. Magn. Reson.* 1998; 131:191–198. [PubMed: 9571092]
- Gochberg DF, et al. Studies of magnetization transfer and relaxation in irradiated polymer gels—interpretation of MRI-based dosimetry. *Phys. Med. Biol.* 2001; 46:799–811. [PubMed: 11277226]
- Gore JC, et al. Measurement of radiation dose distributions by nuclear magnetic resonance (NMR) imaging. *Phys. Med. Biol.* 1984; 29:1189–1197. [PubMed: 6494247]
- Kennan RP, et al. The effects of cross-link density and chemical exchange on magnetization transfer in polyacrylamide gels. *J. Magn. Reson. B.* 1996; 110:267–277. [PubMed: 8867442]
- Lepage M, et al. C-13-NMR, H-1-NMR, and FT-Raman study of radiation-induced modifications in radiation dosimetry polymer gels. *J. Appl. Polym. Sci.* 2001; 79:1572–1581.
- Lepage M, et al. Magnetization transfer imaging for polymer gel dosimetry. *Phys. Med. Biol.* 2002; 47:1881–1890. [PubMed: 12108773]
- Maryanski MJ, et al. Magnetic resonance imaging of radiation dose distributions using a polymer-gel dosimeter. *Phys. Med. Biol.* 1994; 39:1437–1455. [PubMed: 15552115]
- Maryanski MJ, et al. Radiation therapy dosimetry using magnetic resonance imaging of polymer gels. *Med. Phys.* 1996; 23:699–705. [PubMed: 8724743]
- Press, WH., et al. *Numerical Recipes in C: The Art of Scientific Computing*. Cambridge: Cambridge University Press; 1992.
- Tanford, C. *Physical Chemistry of Macromolecules*. New York: Wiley; 1961. chapter 8: multiple equilibria.

Figure 1.
The relaxation rate R_1 versus dose (Gy).

Figure 2.
The pool size ratio p_m/p_f versus dose (Gy).

Figure 3.
The MT rate k_{mf} versus dose (Gy).

Figure 4.
The MT rate k_{fm} versus dose (Gy).