The Effects of Rotational Correlation Time of Paramagnetic Contrast Agents on Relaxation Enhancement: Partial Binding to Macromolecules

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Purpose : To evaluate the effect of rotational correlation time (τ_R) and the possible related changes of other parameters, τ_M, τ_s, and τ_v of gadolinium (Gd) chelate on T1 relaxation enhancement in two pool model.

Materials and Methods : The NMRD (Nuclear Magnetic Relaxation Dispersion) profiles were simulated from 0.02 MHz to 800 MHz proton Larmor frequency for different values of rotational correlation times based on Solomon-Bloembergen equation for inner-sphere relaxation enhancement. To include both unbound pool (pool A) and bound pool (pool B), the relaxivity was divided by contribution from unbound pool and bound pool. The rotational correlation time for pool A was fixed at the value of 0.1 ns, which is a typical value for low molecular weight complexes such as Gd-DTPA in solution and τ_R for pool B was changed from 0.1 ns to 20 ns to allow the slower rotation by binding to macromolecule. The fractional factor f was also adjusted from 0 to 1.0 to simulate different binding ratios to macromolecule. Since the binding of Gd-chelate to macromolecule can alter the electronic environment of Gd ion and also the degree of bulk water access to hydration site of Gd-chelate, the effects of these parameters were also included.

Results : The result shows that low field profiles, ranged from 0.02 to 40 MHz, are dominated by contribution from bound pool, which is bound to macromolecule regardless of binding ratios. In addition, as more Gd-chelate bound to macromolecule, sharp increase of relaxivity at higher field occurs. The NMRD profiles for different values of τ_s show the enormous increase of low field profile whereas relaxivity at high field is not affected by τ_s. On the other hand, the change in τ_v does not affect low field profile but strongly influences on both inflection field and the maximum relaxivity value. The results shows a parabolic dependence of relaxivity on τ_M.

Conclusion : Binding of Gd-chelate to a macromolecule causes slower rotational tumbling of Gd-chelate and would result in relaxation enhancement, especially in clinical imaging field. However, binding to macromolecule can change water enchange rate (τ_M) and electronic relaxation time (T_{1e}) via structural deformation of electron environment and the access of bulk water to hydration site of metal-chelate. The clinical utilities of Gd-chelate bound to macromolecule are the less dose requirement, the tissue specificity, and the better perfusion and intravascular agents.

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Introduction

Like any contrast agent in radiology, magnetic resonance (MR) contrast agents are administrated to a patient in order to enhance the image contrast between normal and diseased tissue and/or to indicate the status of organ function or blood flow (1-4). The signal intensity in ^1H MRI, largely composed of water protons, is dependent on nuclear magnetic relaxation times. Paramagnetic ions, which possess large magnetic moments, have ability to decrease the relaxation times of nearby protons and are commonly used as MR contrast agents. Two types of MR agents are currently available: T1 and T2 agents (5-7). Whereas T2 agents are dependent on relatively simple relaxation mechanism, T1 agents rely on more complicated relaxation process, which is called inner-sphere mechanism (8-9). The term inner-sphere relaxation represents the process that a water molecule binds in the hydration layer of the metal ion and exchanges with the bulk water. The T1 relaxation contribution from the inner-sphere mechanism is known to result from three major parameters: rotational correlation time, water exchange time, and electronic relaxation time T_{1e}. The efficiency of paramagnetic agents, therefore, can be increased by optimizing these parameters and will minimize the necessary dose for patients. Relaxation enhancement through parameter optimization has very practical importance and is very active research area (10-11).

For metal ions such as Gd with long T_{1e}, alteration of the rotational tumbling time is the single most important source of relaxation enhancement. The degree of enhancement possible, which is limited by the values of other parameters such as T_{1e} and τ_M, exceeds that which is realistically available from optimizing any of the other relevant parameters. In general, slowly rotating metal ions give larger gains in relaxation enhancement than fast rotating metal ions. The covalent or noncovalent attachment of a metal ion to a macromolecule can serve a model system to observe the effect (12-13). For example, the binding of Gd-chelate to protein molecule, which has much bigger molecular weight, would result high gain in relaxation enhancement. Protein binding of paramagnetic MR agent was recently observed with new liver-specific MR agents, Gd-EOB-DTPA (14). However, the relaxation enhancement from the binding of Gd-EOB-DTPA to a protein was much less than that of expected values from rigidly attached model system (15).

In this study, the effect of rotational correlation time on relaxation enhancement was investigated basing on inner-sphere mechanism. To be more realistic, two different pools of Gd-chelates are assumed such as unbound and bound pool. Bound pool is a system that Gd-chelates are bound to macromolecules. The rotational correlation time in bound pool is assumed to be slower than that of unbound pool. Since the binding of Gd-chelate to macromolecule can alter the electronic environment of Gd ion and also the degree of bulk water access to hydration site of Gd-chelate, the effects of these parameters were also included in this study.

Materials and Methods

Theory

The relaxation enhancement of mobile water proton by paramagnetic ions is in principle sum of three contributions: intrinsic, inner-sphere and out-sphere contribution.

$$\frac{1}{T1_{observed}} = \frac{1}{T1_{intrinsic}} + \frac{1}{T1_{inner}} + \frac{1}{T1_{outer}} \quad [1]$$

where $T1_{intrinsic}$ is the T1 relaxation time of pure water. The last two contributions are often called as paramagnetic contributions. For a paramagnetic ion at low concentration, $T1_{inner}$ is shortest among three and is so most dominant.

The T1 relaxation contribution from the inner sphere mechanism results from a chemical exchange of the water molecule between the primary coordination sphere of the paramagnetic metal ion and the bulk solvent yielding the following expression:

$$\frac{1}{T_{inner}} = \frac{P_M \cdot q}{T_M + \tau_M} \quad [2]$$

Here P_M is the mole fraction of metal ion, q is the number of water molecules bound per metal ion, T_M is the relaxation time of the bound water protons, and τ_M is the residence lifetime of the bound water. The value of T_M is in turn given by the Solomon-Bloembergen equation (16-17) :

$$\frac{1}{T_M} = \frac{2}{15}\frac{\gamma^2_I g^2 S(S+1)\beta^2}{\gamma^6}\left[\frac{7\tau_C}{(1+\omega^2_S\tau^2_C)} + \frac{3\tau_C}{(1+\omega^2_I\tau^2_C)}\right] \quad [3]$$

where γ_I is the proton gyromagnetic ratio, g is the electronic g factor, S is the total electronic spin of the metal ion, β is the

Bohr magneton, r is the proton-metal ion distance, and ω_S and ω_I are the electronic and proton Larmor frequencies, respectively. The dependence on the latter two quantities makes relaxivity a function of magnetic field as well as other physical and chemical properties. The key feature of paramagnetically induced nuclear relaxation is that the local magnetic field from the electron spin must fluctuate at proper frequencies to stimulate nuclear relaxation. The time scale of these fluctuations is characterized by the overall correlation time τ_c : the characteristic rate of these fluctuations, $1/\tau_c$, is usually dominated by the fastest of three processes :

$$\frac{1}{\tau_c} = \frac{1}{T_{1e}} + \frac{1}{\tau_M} + \frac{1}{\tau_R} \qquad [4]$$

where T_{1e} is the electronic T1 relaxation time, τ_M is the water residence time, and τ_R is the rotational tumbling time of the entire metal-water unit. Electronic T1 relaxation time (T_{1e}) is given as (18)

$$\frac{1}{T_{1e}} = \frac{6}{5}\left(\frac{2D^2}{3} + 2E^2\right)\left[\frac{2\tau_V}{(1+\omega^2_S\tau^2_V)} + \frac{8\tau_V}{(1+4\omega^2_S\tau^2_V)}\right] \qquad [5]$$

This can be rewritten as

$$\frac{1}{T_{1e}} = \frac{0.2}{\tau_S}\left[\frac{1}{(1+\omega^2_S\tau^2_V)} + \frac{4}{(1+4\omega^2_S\tau^2_V)}\right] \qquad [6]$$

and τ_S is now related as follows [19].

$$\tau_S = 0.2 \times \left(\frac{5}{12}\right)[(\tau_V)\left(\frac{D^2}{3} + E^2\right)]^{-1} \qquad [7]$$

where D and E are measure of distortions resulting from octahedral symmetry of the Gd-chelate. This distortions, in turn, lead to transient zero-field splitting (ZFS) of the electronic spin levels and become the major source of electronic relaxation. The physical meaning of τ_S is the magnitude of ZFS at zero field.

NMRD Simulation

The NMRD profiles were simulated from 0.02 MHz to 800 MHz proton Larmor frequency for different values of rotational correlation times based on Solomon-Bloembergen equation for inner-sphere relaxation enhancement. The other contributions are neglected due to their smallness. Gadolinium with S = 7/2 was chosen as a metal ion of interest. Relaxivity, which is relaxation rate per mM concentration of Gd, was estimated in all NMRD simulation. To include both bound pool and unbound pool, the relaxivity was divided by pool A (unbound) and pool B (bound).

$$\frac{1}{T_{inner}} = f \cdot \frac{P_M q}{T^A_M + \tau_M} + (1-f) \cdot \frac{P_M q}{T^B_M + \tau_M} \qquad [8]$$

where $T_M{}^A$ is T1 of bound water of metal ion, which is not attached to macromolecule and $T_M{}^B$ is T1 of bound water of metal ion, which is attached to macromolecule. To allow the different fraction between two pools, fractional factor f was included.

The rotational correlation time for pool A was fixed at the value of 0.1 ns, which is typical value for low molecular weight complexes such as Gd-DTPA in solution and τ_R for pool B was changed from 0.1 ns to 20 ns to allow the slower rotation by binding effect to macromolecule. The fractional factor f was also adjusted from 0 to 1.0 to simulate different binding ratios to macromolecule. The other parameters necessary for NMRD calculation were same for both pools: q = 1, r = 3.13 Å, τ_M = 3 ns, τ_S = 0.1 ns, and τ_V = 40 ps. The number of bound water (q) to Gd-chelate was fixed as one because there exists a fundamental trade-off between relaxation enhancement on one hand and stability and toxicity on the other. That is, chelation of a metal ion with a multidentate ligand such as DTPA forms a very stable and nontoxic complex but allows only one bound water molecule. The distance (r) between bound water protons and the unpaired electron spin of a metal ion was fixed as 3.13 Å, which is typical value for Gd-DTPA with assumption that the binding to macromolecule does not deform the metal-chelate much and so distance is kept the same.

The remaining parameters, water exchange time (τ_M) and electronic parameters τ_S and τ_V, are initially set to τ_M = 3 ns, τ_S = 0.1 ns, and τ_V = 40 ps. These parameters can be affected by binding to macromolecule. That is, by binding to macromolecule, the access of bulk water to hydration site of metal-chelate can be hindered. The electronic parameters, τ_S and τ_V, which determine electronic T1, are resulted from a transient zero-field splitting (ZFS) of the spin levels induced by collisions between the chelate and bulk water molecules. Binding to macromolecule can change the collision patterns and result in changes of these values. Therefore, these variables are allowed to change and the effects are also investigated.

All simulations were performed using PC-based symbolic calculation package (Mathcad Plus 5.0, MathSoft Inc., U.S.A.)

Results

Figure 1 shows calculated NMRD profiles for different values of the rotational correlation time τ_R for bound pool only. The values for other parameters typical of Gd are utilized. The result for τ_R = 0.1 ns shows typical profile pattern. At low magnetic field up to 30 MHz, relaxivity is constant and then disperses into lower relaxivity along with the field strength. However, as τ_R increases, relaxivity starts to increase at 40 MHz and reaches maximum at 400 MHz and then decreases again at higher field. This result clearly shows that the binding effect of Gd-chelate, therefore, is important between 40 MHz (~ 1.0 Tesla) and 600 MHz (~ 14 Tesla). This magnetic field region includes the clinical imaging field (for instance, 1.5 Tesla).

The calculated NMRD profiles for total relaxivity of both bound and unbound pools are shown in Figure 2 as a function of different binding ratios. τ_R for Gd-chelate bound to macromolecule was set to 10 ns and τ_R for unbound pool was 0.1 ns. The other parameters were set to typical values for Gd-chelate. The result shows that low field profiles, ranged from 0.02 to 40 MHz, are dominated by contribution from bound pool, which is bound to macromolecule regardless of binding ratios. However, as more Gd-chelate bound to macromolecule, sharp increase of relaxivity at higher field occurs. Overall shape of this relaxivity peak is similar to Figure 1, which suggests that the contribution from bound pool is also dominant in high field region.

The effects of different electronic parameters are shown in Figure 3 and 4. The NMRD profiles for different values of τ_s (Fig. 3) show the significant increase of low field profile whereas relaxivity at high field is not affected by τ_s. The calculated NMRD profiles in Fig. 3 are obtained as a function of different τ_s ranging from 0.01 to 10 ns. Another point is that the magnetic field, which shows maximum relaxivity, shifts to lower field as τ_s increases. Larmor frequency showing maximum relaxivity was 140 MHz (3.2 Tesla) for τ_s = 1ns and 400 MHz (9.4 Tesla) for τ_s = 0.01 ns. However, the inflection in the profile near 10 MHz is seen to keep same regardless of selected τ_s values. On the other hand, the change in τ_v (Fig. 4) does not affect low field profile but strongly influences on both inflection field and the maximum relaxivity value. By increasing τ_v value from 20 ps to 100 ps, the maximum relaxivity increases and the corresponding magnetic field shifts to lower field. That is, the maximum relaxivity and the corresponding field for τ_v = 100 ps are 13.54 $mM^{-1}S^{-1}$ and 140 MHz whereas the values for τv = 20 ps are 9.05 $mM^{-1}S^{-1}$ and 300 MHz respectively. Also, the inflection field shifts to lower field as τ_v increases.

Figure 5 shows calculated NMRD profiles for different val-

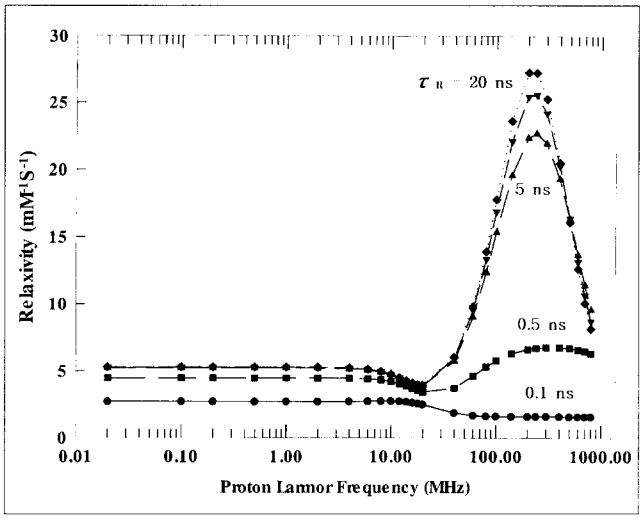

Fig. 1. Calculated T1 NMRD profiles for different values of τ_R. The inner-sphere contribution was utilized with the values for the other parameters typical of Gd-chelate: q = 1, r = 3.13 Å, τ_M = 3 ns, τ_v = 40 ps, τ_s = 0.1 ns. As τR increased, T1 relaxivity enhancement occurs mostly between 30 MHz and 800 MHz, which include conventional imaging field.

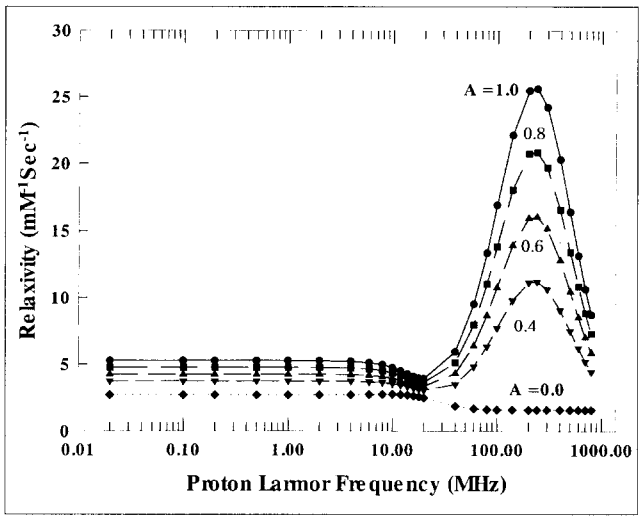

Fig. 2. Calculated NMRD profiles for two pool model. A represents the ratio between unbound and macromolecule-bound pool. τ_R for Gd-chelate bound to macromolecule was set to 10 ns and τ_R for unbound pool was 0.1 ns. The values of other parameters were same as Fig 1. As more Gd-chelates were bound to macromolecule, T1 relaxivity enhancement observed mostly between 30 MHz and 800 MHz,

ues of τ_M of binding factor A = 0.4 (40 % binding). Two interesting results are: (1) τ_M has optimum values, which increases relaxivity further and (2) as τ_M increases, the peak width of relaxivity reduces. Relaxivity in NMRD profile reaches its maximum value at τ_M = 30 ns. If water exchange is much faster than the value of 3 ns (that is if τ_M = 0.3 ns), the relaxivity is significantly reduced at high field region suggesting that high field profile is mostly governed by unbound pool of τ_M = 3 ns. As water exchange becomes slower than 3 ns, relaxivity starts to increase until reaching to maximum value. The optimum value of τ_M is therefore 30 ns in calculated NMRD profile. On the other hand, if water exchange is much slower than 3 ns (that is if τ_M = 100 and 300 ns), the relaxivity is again reduced at high field region. The second finding on the effect of water exchange rate was that as τ_M increases, the peak width of relaxivity reduces. This result suggests that the water exchange rate has a "tuning" effect on relaxation enhancement at high field regions.

One of the experimental evidences of the results obtained in this NMRD simulations is shown in Figure 6 (adopted from Ref. 15). Fig. 6 shows 1/T1 NMRD profiles, which were obtained on an IBM field cycling relaxometer operating at proton Larmor frequencies from 0.02 MHz to 50 MHz, for 0, 5, 10% human serum albumin (HSA) solutions doped with 1 mM Gd-EOB-DTPA. Whereas the NMRD data for aqueous solution of 0% HSA (filled triangles) show no evidence for relaxation enhancement between 10 and 50 MHz range, 5% (filled circles) and 10% (filled squares) HSA data show increasing enhance-

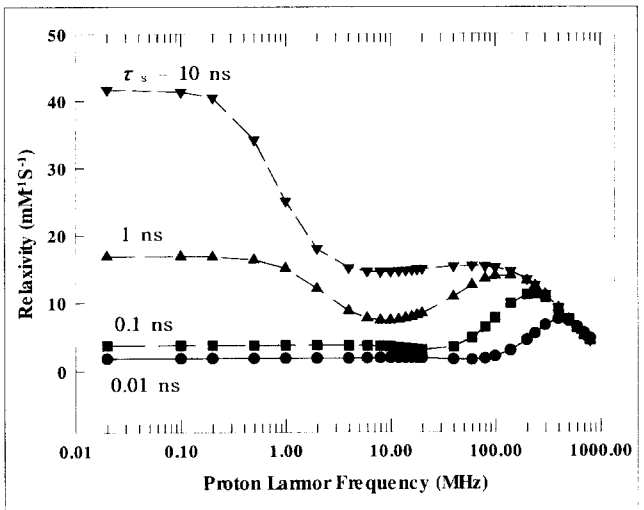

Fig. 3. Calculated NMRD profiles of binding ratio A = 0.4 for different values of T_{1e} at zero magnetic field (τ_s). The values for the other parameters were typical of Gd-chelate: q = 1, r = 3.13 Å, τ_v = 40 ps. The τ_R was 10 ns for bound pool and 0.1 ns for unbound pool. As τ_s increased, low field profiles were significantly increased whereas high field profiles were not affected.

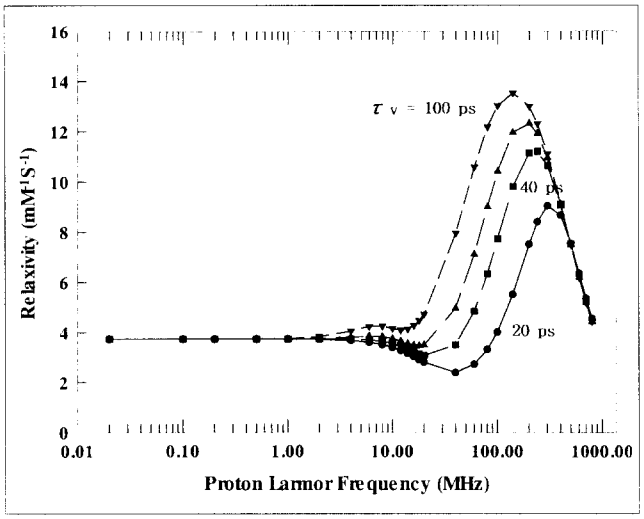

Fig. 4. Calculated NMRD profiles of binding ratio A = 0.4 for different values of τ_v. The τ_R was 10 ns for bound pool and 0.1 ns for unbound pool. The values for the other parameters were typical of Gd-chelate: q = 1, r = 3.13 Å, τ_s = 0.1 ns. As τ_v increased, the position of relaxation enhancement peak moved to lower magnetic field.

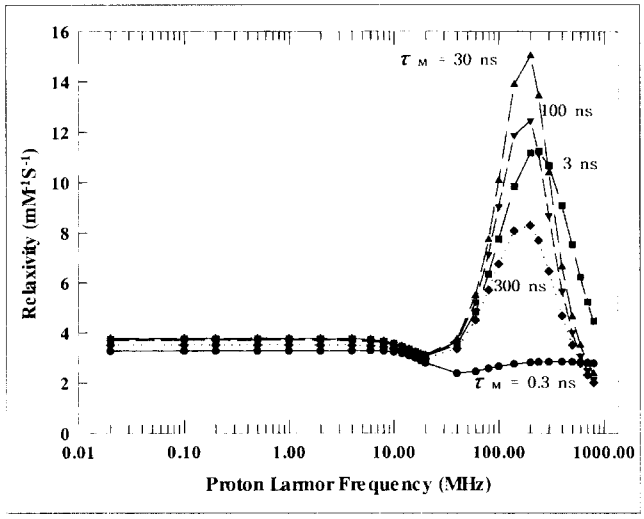

Fig. 5. The NMRD profiles for different values of τ_M of binding ratio A = 0.4 (40% binding). The τ_R was 10 ns for bound pool and 0.1 ns for unbound pool. The values for the other parameters were typical of Gd-chelate: q = 1, r = 3.13 Å, τ_v = 40 ps, τ_s = 0.1 ns. The τ_M ranged from 0.3 ns to 300 ns. As τ_M increased, the peak width of relaxation enhancement reduced. However, peak height, which represents further relaxation enhancement, reached to maximum value at τ_M = 30 ns and started to reduce as τ_M was increased further.

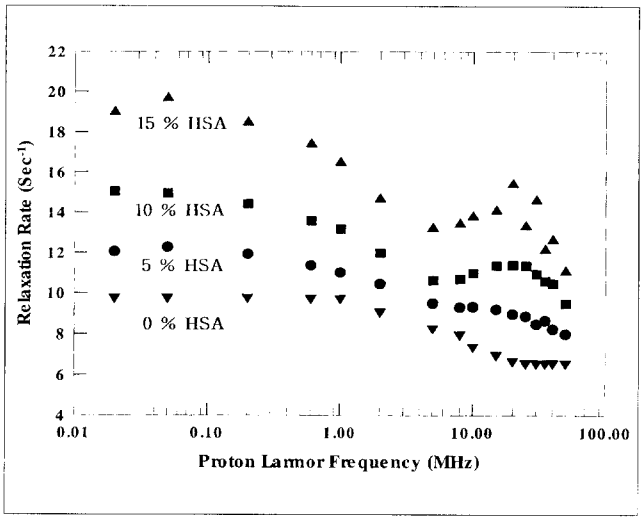

Fig. 6. Experimental NMRD profiles for different human serum albumin (HSA) bidings. As more Gd-EOB-DTPA's were bound to HSA, relaxivity increased at all fields with relaxation enhancement peak (adapted from Chang Y et al, The Proc. 5th Int Soc Magn Reson Med 1997 Vol. 3, pp 1588).

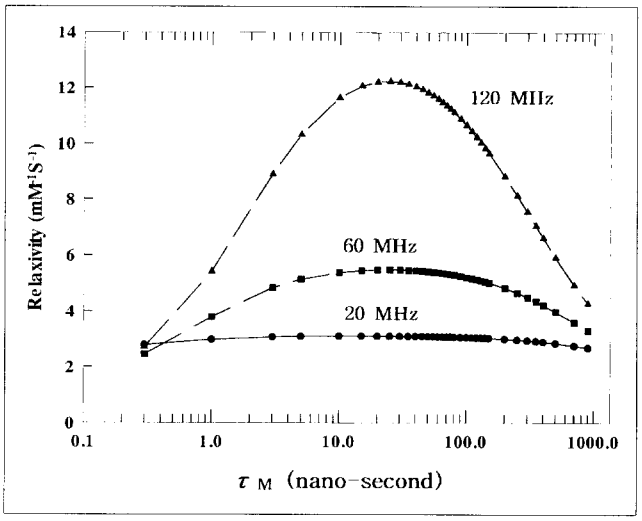

Fig. 7. Calculated relaxivities at different proton resonance frequencies as a function of τ_M for two pool model of binding ratio A = 0.4. The τ_R was 10 ns for bound pool and 0.1 ns for unbound pool. The values for the other parameters were typical of Gd-chelate: q = 1, r = 3.13 Å, τ_v = 40 ps, τ_s = 0.1 ns.

ments over the same range. The results from Fig. 6 suggest that more protein binding causes more relaxation enhancement, which is consistent with our simulations and the electronic parameters might be changed by binding. This is also consistent with our simulation results with different τ_s. However, it is difficult to see the effect of different water exchange rate (τ_M) just with limited experimental data as shown in Fig. 6.

Discussion and Conclusion

For Gd-chelate, which has relatively long electronic T_{1e}'s, alteration of the rotational correlation time (τ_R) is the single most important source of relaxivity enhancement. This is well demonstrated in Fig. 1. Two basic methods exist to alter the rotational mobility of Gd-chelate in vivo. First method is a covalent attachment of the Gd-chelate to a larger molecule such as a protein or antibody before injection. The other way is a noncovalent binding of the chelate in tissue to macromolecules. However, it is often observed that only some of Gd-chelate is bound to macromolecules. The role of τ_R in relaxivity enhancement is still important in case of some Gd-chelate bound to macromolecuels. Also it is important to note that the relaxivity enhancement peak occurs at the magnetic field, where high field clinical MRI often performed. Therefore, optimizing τ_R, limited by the values of τ_M, τ_s and τ_v, has very clinical importance for efficient use of contrast agents.

Although the binding to macromolecules would result in relaxation enhancement through slower rotation of Gd-chelate, the binding would also cause the change in other important parameters such as τ_M, τ_s and τ_v. These parameters can alter the degree of relaxation enhancement resulting from binding effect of Gd-chelate to macromolecules. In general, T_{1e} in terms of τ_s and τ_v in part determines the time scale of the fluctuations in the unpaired electrons' s magnetic field at the nucleus and are included in the spectral density portion of the Solomon-Bloembergen equations. On the other hand, τ_M can be important in modulating either the spectral densities or the efficiency of the chemical exchange of water between chelate-bound and bulk environment. The source of electronic T1 (T_{1e}) is collisions between the chelate and solvent molecules. The collisions are thought to induce a transient zero-field splitting(ZFS) of the electronic spin levels and then the induced ZFS cause the electrons to relax. The degree of electronic relaxation is governed by the strength of ZFS, which represented with τ_s and by the τ_v, which characterizes the ZFS modulation. Though electron spin relaxation with transient ZFS cannot be extended directly to less symmetrical Gd-chelate, the relationship between ZFS and T_{1e} is thought to be general : an increase in ZFS will lead to shorter T_{1e} values and reduced relaxivity. The need for long T_{1e} therefore suggests to minimize ZFS in Gd-chelate. From the calculated NMRD profiles with different

values of τ_V, it is found that the value of τ_V determines the magnetic field strength at which T_{1e} begins to increase with field. However, the exact physical nature of τ_V needs to be studied further.

The binding of Gd-chelate to a macromolecule could influence the water exchange time (τ_M) directly, via hydrogen-bonding interactions with the bound water or steric blocking of the water exchange pathway to the bulk water, or indirectly, via alteration of the ligand structure (20-22). Although it is difficult to predict the exact nature of the influence of binding effect on τ_M, the behaviors of NMRD profiles on different exchange rates can be deduced from this study. If τ_M becomes short or too long due to binding to macromolecule, τ_M reduces the relaxation enhancement resulting from slower rotation of Gd-chelate. On the other hand, some range of τ_M will assist further refinement of relaxation enhancement resulting from slower rotation of Gd-chelate. Figure 7 shows a parabolic dependence of relaxivity on τ_M. Therefore, the water exchange time does have importance as a final optimization parameter for immobilized system such as Gd-chelate bound to macromolecule.

In conclusion, the binding of Gd-chelate to a macromolecule causes slower rotational tumbling of Gd-chelate and would result in relaxation enhancement especially in clinical imaging field. However, binding to macromolecule can change water enchange rate (τ_M) and electronic relaxation time (T_{1e}) via structural deformation of electron environment and the access of bulk water to hydration site of metal-chelate. Therefore, it is necessary to consider not only τ_R optimization but also related τ_M and T_{1e} optimization to design the paramagnetic contrast agents having high efficiency. The clinical utilities of MR contrast agents of high efficiency are several. First, the necessary dose for clinical examination can be significantly reduced. This will provide better safety and less cost. Second, as Gd-chelate binds to macromolecule, the agent becomes more organ specific. This tissue specific MR agent will give more diagnostic informations including organ function. Finally, the complex of Gd-chelate and macromolecule tends to have longer intravascular half life. This blood pool effect of Gd-chelate bound to macromolecule makes the complex as intravascular MR agent, which is important for perfusion imaging and contrast enhanced MR angiography.

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거대분자에 부분적으로 결합한 상자성 자기공명 조영제의 회전속도가 이완증강에 미치는 영향

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목적: 두 개의 다른 화학적 환경하에 있는 gadolinium 자기공명조영제에서 무작위적 회전속도(τ_R) 및 연관된 parameter들(τ_M, τ_s, τ_v)의 변화가 T1 이완증강에 미치는 영향을 알아보고자 하였다.

대상 및 방법: 조영제의 회전속도의 변화에 따른 양성자의 해당 공명주파수에서의 자기이완 시간을 결정하는 NMRD (Nuclear Magnetic Relaxation Dispersion) profile들을 0.02 MHz 로부터 800 MHz까지에서 Solomon-Bloembergen 방정식을 이용하여 계산하였다. 두 개의 다른 조영제들의 환경, 즉 일부 조영제는 거대분자에 결합하여 조영제의 회전 속도가 느려지고 나머지 조영제는 결합하지 않아 원래의 회전속도를 유지하는 모델을 사용하였다. 결합하지않은 조영제의 경우 회전속도는 0.1 ns 으로 거대분자에 결합한 조영제의 경우 회전속도는 0.1 ns부터 20 ns 까지 가변하며 그 영향을 조사하였으며 결합한 조영제와 결합하지 않은 조영제의 비율을 달리하며 조영제의 비율에 따른 이완증강 상의 변화를 살펴보았다. 또한 조영제가 거대분자에 결합하는 경우 결합된 조영제의 전자적 환경 및 조영제의 물분자 결합 위치에서의 물분자의 교환정도에 변화를 야기 할 수 있기 때문에 이러한 parameter들이 변화하는 경우 전체 이완증강에 미치는 영향을 조사하였다.

결과: 0.02 MHz부터 40 MHz 까지의 낮은 자장 영역에서는 결합비율에 상관없이 거대분자에 결합된 조영제가 전체 조영증강에 미치는 영향이 가장 크다는 결과를 얻었다. 하지만 결합비율이 증가할수록 높은 자장영역에서 큰 폭의 조영증강 효과가 나타났고 이러한 조영증강 효과는 결합비율에 비례하였다. 한편 조영제의 전자적인 환경의 변화를 나타내는 τ_s 와 τ_v 의 변화가 조영증강에 미치는 영향은 먼저 τ_s 의 변화가 주로 낮은 자장영역에서의 조영증강에 영향을 미치는 반면 τ_v 의 변화는 높은 자장영역에서 조영증강이 시작되는 자장과 최대 조영증강치에 주로 영향을 미치는 결과를 나타내었다. 물분자의 교환속도를 나타내는 τ_M 의 변화는 물분자의 교환속도가 너무 빠르지도, 너무 느리지도 않는 한도 내에서만 추가적인 조영증강 효과를 가져온다는 사실을 규명하였다.

결론: Gadolinium 자기공명조영제의 일부라도 거대분자에 결합하는 경우 조영제의 회전속도가 느려져서 결과적으로 현재 임상적으로 많이 사용되는 자기장의 세기를 포함하는 자장대에서 큰 폭의 조영증강 효과를 유발할 수 있다. 하지만 이러한 결합은 조영증강 정도를 결정하는 다른 parameter들의 변화를 유발할 수 있고 이러한 변화는 회전속도에 의한 조영증강 효과에 추가적인 조영증강 효과를 가져올 수도 있지만 회전속도에 의한 조영증강 효과를 감소시킬 수도 있다는 사실에 유의하여야 한다. 본 연구에서 제안된 거대분자와 결합한 Gd 자기공명조영제 시스템의 임상적 유용성은 먼저 검사에 필요한 용량의 감소와 조영제의 조직특성의 증가 그리고 관류영상 획득 및 조영증강 자기공명 혈관조영술에 매우 우수한 효과를 나타낼 것으로 기대된다.

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