ORIGIN OF THE NONEXPONENTIALITY OF THE WATER PROTON SPIN RELAXATIONS IN TISSUES

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ABSTRACT An attempt to explain the nonexponential recovery of the water proton spin magnetization in tissues is presented. The origin of this effect is the nonhomogeneity of the material and the distribution of slow diffusion correlation times. This proposal is based on a dispersion study of the tissue water proton spin relaxation time in the rotating frame.

It was proposed recently (1) that the water proton spins in tissues are relaxed by three dynamic modes of water protons, Fig. 1. Two of these modes, i.e., the fast diffusion of water in the free state, and the slow reorientation of bound water in the hydration layer of large molecules, are quite well understood and have been discussed by several research groups (2). The third mechanism, exchange diffusion, is more problematic. Although its existence was assumed for some time, it was directly observed only recently through a dispersion study of spin-lattice relaxation in the rotating frame (3). At that time we incorrectly proposed that this mechanism is the exchange of protons among different water molecules. It is clear now that it is the exchange of water molecules to and from the hydration layer by slow diffusion. The correlation time τ_e for this "exchange" diffusion of $\sim 10^{-5}$ s may be considered to be the residence time of a water molecule in the hydration layer. This process is fast on the scale of any contribution to T_1; e.g., τ_e is much shorter than the T_1 of the hydration layer water (~ 50 ms) and of the free state water (~ 1 s). It should be noted also that it is much longer than the correlation time for the reorientation of water molecules in the hydration layer ($\sim 10^{-8}$ s). This slow diffusion is thus capable of strongly mixing the water molecules in different environments. For this reason, the fast exchange approach is valid in evaluating T_1 in tissues. However, since $\tau_e\omega_0 \simeq 10^3$, the exchange diffusion is much too slow to relax directly the Zeeman energy at high fields.

Because of the strong mixing, the water proton spin-lattice relaxation at high fields would be exponential if all the water compartments in tissues were equal. If this is not the case, a distribution of T_1 should be observed. When the free induction decay (FID) amplitude is studied at a short time ($t < 30$ μs) after the 90° pulse, a strong nonexponentiality is observed. This is due to the proton FID of large molecules which have,

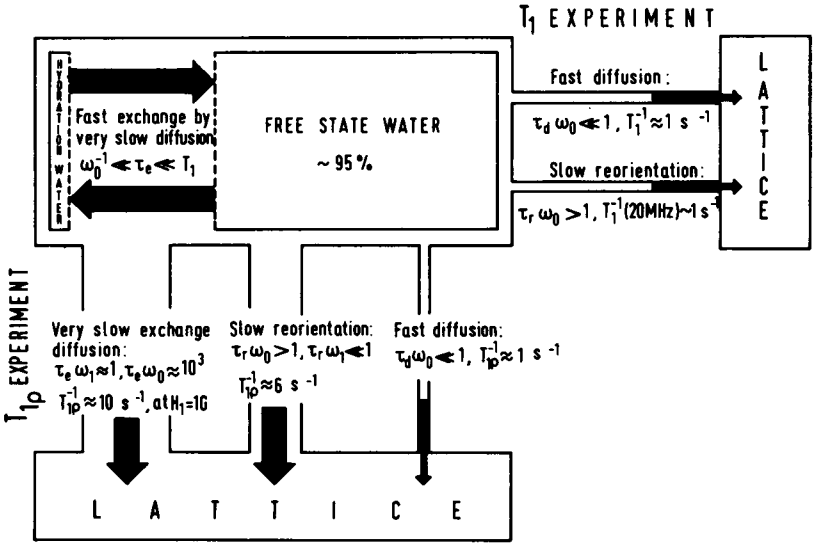

FIGURE 1 The three relaxation processes and their contribution to the high field and the rotating field Zeeman relaxation. The numerical values shown for the relaxation rates are approximative.

in general, a shorter T_1. When the large molecules' proton FID does not contribute anymore, typically at $t > \frac{1}{3}$ ms, T_1 becomes apparently exponential, and remains exponential to about 3 ms. At still greater times, T_1 becomes longer (R. T. Thompson, unpublished work). This shows that a distribution of compartments exists in tissues. For example, the intercellular water should have proportionally less bound water than the intracellular water, and thus have longer T_1. This behavior can be followed by a 90°-90° pulse sequence but is very hard to see by the more standard 180°-90° sequence.

Thus, the strong mixing by exchange diffusion, Fig. 1, forces the water proton magnetization to decay in each compartment i in a tissue with a single spin-lattice relaxation time:

$$1/T_{1i} = b_i(1/T_1)_r + (1 - b_i)(1/T_1)_d, \tag{1}$$

where b_i is the fraction of the bound water in compartment i. The rotational relaxation rate within hydration layers $(1/T_1)_r$ is assumed to be the same throughout the tissue. The fast diffusion relaxation rate of the free state water is $(1/T_1)_d$ and is also assumed to be constant throughout all the tissue. It should be noted that although there is a distribution of the rotational correlation times within each compartment, as well as fast diffusion correlation times, the strong mixing averages out these distributions.

The spin-spin relaxation time (T_2) of water proton spins in tissues is different from T_1 in that it is sensitive to the spectral density of water modes at zero frequency also and, as a result, the very slow diffusion responsible for exchange contributes directly to it. Since there is a distribution of the exchange diffusion correlation times, FID is more "nonexponential" than the recovery of the longitudinal magnetization. Such be-

havior was indeed observed (5, 6). However, the exchange diffusion is still a strong mixing process for the rotational and fast diffusion contribution to T_2. Thus, T_2 should be similar to T_1 with respect to these two processes. In contrast to T_1 however, because of the effect of exchange diffusion, T_2 is a distribution also in each compartment

$$1/T_{2i} = \sum_j A_{ji}\tau_{eji} + b_i(1/T_2)_r + (1 - b_i)(1/T_2)_d, \tag{2}$$

where i stands for the compartment and $\sum_j$ represents the distribution of slow diffusion correlation times. When we consider that $1/T_2$ is a distribution within each compartment and that in addition there is a distribution of compartments, it is not surprising that FID is nonexponential. For this reason the apparent three magnetization "fractions," each with a different T_2, should not be identified by the three types of water magnetization (extracellular, hydration and free water), nor should they be considered an argument against the fast exchange assumption (5).

The decay of the spin-locked magnetization has a nonexponential character as well. This nonexponentiality is similar to that of T_2 in that it is possible to construct a $20 \pm 5\%$ magnetization "fraction" which decays with a longer $T_{1\rho}$. Here again the exchange diffusion mixes the bound water and the free state water. As in the case with T_2, the exchange diffusion itself (1) contributes to $1/T_{1\rho}$, Fig. 1, which thus displays the distribution of τ_e in each compartment through the term

$$\sum_j A_{ji} \cdot [\tau_{eji}/(1 + 4\tau_{eji}^2\omega_1^2)].$$

The total spin-lattice relaxation rate in the rotating frame due to all mechanisms (1) is:

$$\left[\frac{1}{T_{1\rho}}\right]_i = \sum_j \frac{A_{ji}\tau_{eji}}{1 + 4\tau_{eji}^2\omega_1^2} + b_i\left[\frac{1}{T_{1\rho}}\right]_r + (1 - b_i)\left[\frac{1}{T_{1\rho}}\right]_d. \tag{3}$$

Since $\omega_1\tau_r \simeq 0$ for the rotational mode in the hydration layer, the rates $[1/T_{1\rho}]_r$ and $[1/T_{1\rho}]_d$ are the same as $[1/T_2]_r$ and $[1/T_2]_d$, respectively. Consequently, at small spin-locking fields ($\tau_e\omega_1 < 1$), the rate $[1/T_{1\rho}]_i$ should have almost the same nonexponential character as $1/T_2$.

The nonexponentiality of the decay of the spin-locked water proton magnetization has been observed to occur in all tissues studied. It was always possible to divide graphically the magnetization into a smaller component ($20 \pm 5\%$), which decayed with a longer $T_{1\rho}$, and into a larger component, which decayed with a shorter $T_{1\rho}$. It should be noted that such graphical construction is quite arbitrary. It was done to investigate qualitatively the origin of the nonexponentiality. Since the nonexponentiality is not very obvious in most experiments $T_{1\rho}$ (as well as T_2) is determined as a weighted average of the long and short $T_{1\rho}$. The experiments were done with C3H (Jackson Laboratory, Bar Harbor, Maine) mice tissues. The sample preparation is

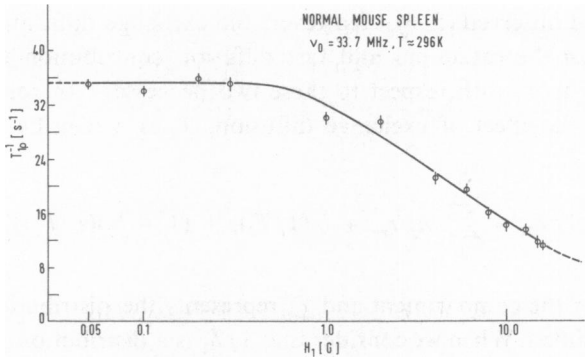

FIGURE 2 The dispersion of the mouse spleen water proton $T_{1\rho}^{-1}$. The rates at $H_1 < \frac{1}{2}$G are not very accurate (±15%). Average $T_{1\rho}^{-1}$ are shown (see text).

described in ref. 4. Both the spin-locking $T_{1\rho}$ experiment and the T_2 measurement were performed with the use of the Spin-Lock Electronics Coherent Spectrometers model CP2 (Spin-Lock Electronics, Missassauga, Ontario).

The proton magnetization was spin-locked by a 90° pulse, followed immediately by a $\pi/2$ phase shifted radio frequency pulse of variable amplitude. The Meiboom dispersion was measured with the Carr-Purcell sequence which has been modified as proposed by Meiboom and Gill (CPMG) (7). The CPMG pulse train was originally employed to remove the effect of nonhomogeneous broadening for the ^{17}O enriched water (8). It has been shown by Ostroff and Waugh (9) to be equivalent for protons to a spin-locking sequence with an effective radio frequency (RF) field $\overline{H}_1 = 59/t_p$ in gauss, where $2t_p$ is the CPMG 180° pulse spacing in microseconds. The effective field picture holds whenever T_2 is much larger than the pulse spacing. In tissues, where T_2 is typically 50 ms, the condition is fulfilled when t_p is <1 ms. Such a sequence then measures $T_{1\rho}$ at small ω_1. While spin-locking in tissues is convenient at RF fields between $1 < H_1 < 10$ G, the CPMG sequence works best at 180° spacing larger than 100 μs, corresponding t_o rotating frame fields which are smaller than 1 G.

The complementarity of $T_{1\rho}$ dispersion and of Meiboom T_2 dispersion is shown in Figs. 2 and 3. For example, the rate T_2^{-1}, at $2t_p = 400\,\mu$s, of 30 ± 2 s^{-1} corresponds

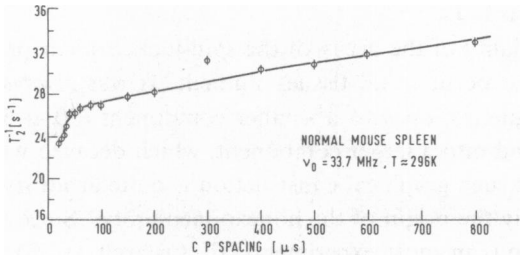

FIGURE 3 The Meiboom dispersion of mouse spleen water proton T_2^{-1}. Average values are shown (see text).

to $T_{1\rho}^{-1}$ at an effective H_1 of 0.3 G. The value of $T_{1\rho}^{-1}$ at such a rotating field was measured to be 35 ± 4 s^{-1}, see Fig. 2. It should be noted that both $T_{1\rho}$ and T_2, in experiments shown in Figs. 2 and 3, were obtained without considering the small magnetization component. However, since the reproducibility is good, the average values shown are acceptable representatives of true distributions.

It should be noted that the exchange of protons among different water molecules would result in qualitatively the same T_2^{-1} and $T_{1\rho}^{-1}$ dispersions. However, since the corresponding proton exchange correlation time of 10^{-5} s is two orders of magnitude shorter than in pure water (8) such a possibility seems remote.

The recovery of the spin-locked magnetization, in other words its decay to zero value, was observed to be nonexponential in all tissues studied. In the muscle tissue the magnetization was graphically decomposed into a large (80 ± 5%) and a small "component." Both components relax differently (Figs. 4 and 5). The large magnetization relaxes with the shorter relaxation time. An approximate relation is $3T_{1\rho}$ (short) $\simeq T_{1\rho}$ (long). The main point of this experiment is the observation that the two magnetization components relax with $T_{1\rho}$'s which remain considerably different in the limit $\omega_1 \to \infty$. However, in this limit the small magnetization "component" becomes slightly smaller. It changes from 20 ± 5% to 12 ± 5% as H_1 is increased from 1 to 10 G. As $\omega_1 \to \infty$, Eq. 3 becomes

$$[1/T_{1\rho}]_i = b_i[1/T_{1\rho}]_r + (1 - b_i)[1/T_{1\rho}]_d. \tag{4}$$

In this limit the distribution of exchange diffusion processes is effectively removed from the relaxation. For this reason the nonexponentiality of $T_{1\rho}$ at $\omega_1 \to \infty$ and T_1 should be similar. The considerably different limiting values of $T_{1\rho}^{-1}$ of large

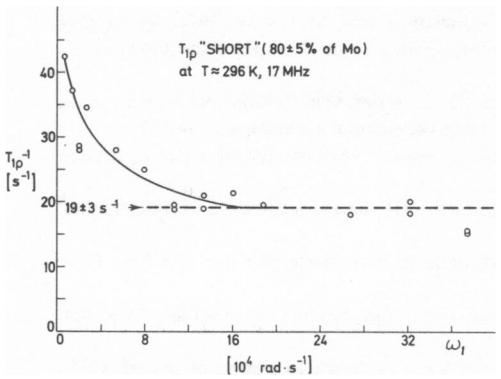

FIGURE 4

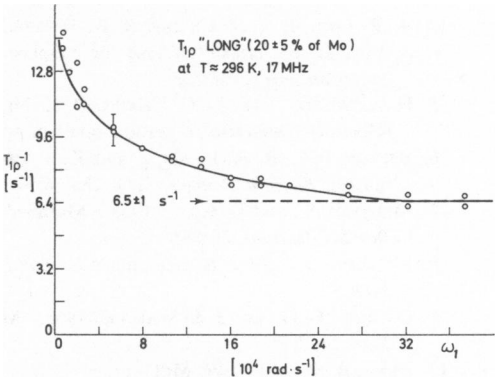

FIGURE 5

FIGURE 4 The mouse muscle water proton $T_{1\rho}$ dispersion of the large "component" of the magnetization 80 ± 5% (which decays with shorter $T_{1\rho}$ than the small component). Note that the size of the components changes slightly with ω_1.

FIGURE 5 The mouse muscle water proton $T_{1\rho}$ dispersion of the small component of the magnetization 20 ± 5%.

and small magnetization components are indicating that a large contribution to the nonexponentiality is compartmental. The rate $T_{1\rho}^{-1}$ of 6.5 ± 1 s^{-1} belongs to the small component, which is identified as mainly due to the intercellular water, since the intercellular compartments have on average much smaller b_i. Tentatively $<b_i>_{intra} \simeq 3 <b_i>_{inter}$. The above observation is qualitatively in agreement with the observed nonexponential FID (7, 8). In the literature however, the effect of the exchange diffusion was neglected.

In summary, the nonexponentiality of the water proton longitudinal magnetization recovery and of FID is the result of a variation of the relative percentage of the bound water in various tissue compartments. In addition, the distribution of slow "exchange" diffusion contributes to the nonexponentiality in the case of T_2 and $T_{1\rho}$.

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