NUCLEAR MAGNETIC RESONANCE OF TISSUE ^{23}Na

II. THEORETICAL LINE SHAPE

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ABSTRACT The theoretical line-shape function of the nuclear magnetic resonance (NMR) signal of ^{23}Na in biological tissue (and other unoriented systems) was obtained under the following conditions: (*I*) there occur two states of ^{23}Na in the system, (*II*) the exchange of ^{23}Na between the two states is rapid (but not too rapid), (*III*) in the absence of exchange, the ^{23}Na in one state is characterized by a single transverse relaxation time T_2 and a single Larmor frequency, and (*IV*) in the absence of exchange, the ^{23}Na in the other state possesses (*a*) two different values of T_2 and/or (*b*) more than one Larmor frequencies in the first order perturbation effect. The theoretical signal obtained consists of two Lorentzian components, which are centered at the same frequency, but characterized by different T_2. Only the narrower component, comprising 40% of the total intensity, is visible, when the fast T_2 is sufficiently short. The theoretical line-shape function of ^{23}Na signal was also calculated for oriented systems in which the above conditions are fulfilled.

INTRODUCTION

The NMR signal of ^{23}Na in biological tissue is quite different from that in its chloride solution. The main features of the signal of tissue ^{23}Na are: (*i*) the integrated intensity is 30–50% (in most tissues) of the intensity expected from the Na content (1–8), (*ii*) the ^{23}Na in tissue has two different transverse relaxation times T_2 (slow T_2 = 9–14 ms and fast T_2 = 0.7–1.1 ms in rat and rabbit tissues) (3, 9, 10). According to the interpretation presented by Cope (1, 2, 9), the invisible steady-state resonance and the fast T_2 of tissue ^{23}Na correspond to the complexed ^{23}Na, which is in slow exchange with the ^{23}Na in free solution.

However, it was shown, in several systems other than biological tissue, that the ^{23}Na signal reflects quadrupole interactions and cannot be explained by Cope's hypothesis (11–13). Shporer and Civan (11) offered an alternative interpretation that the observed signal of tissue ^{23}Na also reflects quadrupole interactions and does not imply the binding of the bulk of tissue Na^+. In a preceding paper (14), we showed that this is, in fact, the case for liver tissue.

On the basis of the theory for the quadrupole relaxation in systems with a slow correlation time, Berendsen and Edzes (10) proposed that the observed resonance of

tissue ^{23}Na takes place because (*i*) in any region, in tissue, of 100 Å, the fluctuating field gradients do not average zero, and (*ii*) diffusion of Na^+ occurs between regions of different average field gradients, and the average field gradients vary slowly with time. According to this interpretation, there is only one species of Na^+ in tissue.

However, the ability to depress the resonance intensity of tissue ^{23}Na was not found in the supernatant fraction; it was exclusively localized in particulate fractions (14). We can now suppose more properly two states of tissue ^{23}Na. The ^{23}Na in one state will be present mostly or exclusively in the liquid phase of tissue and characterized by a single T_2 and a single Larmor frequency, if the exchange of the nuclei between the two states is absent. The ^{23}Na in the other state will interact with the electric-field gradients at the surface of (or within) the membranous components (or other enormous assemblies of molecules or atoms) of tissue. In order to explain the observed signal of tissue ^{23}Na, (*i*) the exchange of ^{23}Na between the two states should be rapid (but not too rapid), and (*ii*) in the absence of exchange, the ^{23}Na in the latter state should possess (*a*) two different T_2 and/or (*b*) more than one Larmor frequencies in first order perturbation effect. Under these suppositions, a theoretical line-shape function of the ^{23}Na resonance of tissue can be obtained, which well explains the observed data. The purpose of the present paper is to show this.

THEORY

The following conditions will be assumed. *Condition I:* There occur two states of ^{23}Na in tissue. The ^{23}Na in one state (state A) may be present mostly or exclusively in the liquid phase of tissue. The ^{23}Na in the other state (state B) may interact in some way with membranous components (or other enormous assemblies of molecules or atoms) in tissue. State B does not necessarily represent a bound state. *Condition II:* The exchange of ^{23}Na between the two states is rapid, but not too rapid. *Condition III:* (For state A) $\tau_c \ll \omega_L^{-1}$ (τ_c, the correlation time for the fluctuating field gradients at the position of the ^{23}Na nucleus; ω_L, the Larmor angular frequency), and the fluctuating field gradients average to zero during a time sufficiently shorter than T_2. In the absence of exchange, the ^{23}Na in state A is accordingly characterized by a single T_2 and exhibits a single Lorentzian absorption signal centered at ω_L. *Condition IV:* (For state B) (*a*) $\tau_c \gtrsim \omega_L^{-1}$, but τ_c is not too long, and/or (*b*) the fluctuating field gradients at the nucleus do not average to zero during a period comparable to τ_B (τ_B, the mean lifetime for a stay in state B). In the absence of exchange, the ^{23}Na in state B is accordingly characterized by either two different T_2 (condition IV *a*) or a single T_2 (condition IV *b* and not IV *a*). Under condition IV *b*, the transitions $\pm 3/2 \leftrightarrow \pm 1/2$ of the ^{23}Na in state B have continuously distributed Larmor frequencies when the system has no macroscopic orientation (in oriented systems, where condition IV *b* is always fulfilled, each of these transitions has either a single Larmor frequency ($\neq \omega_L$) or continuously distributed Larmor frequencies); their normalized line-shape functions without dipolar broadening will be denoted by $f_+(\omega)$ and $f_-(\omega)$ (ω, the angular frequency). Each of the transitions $\pm 3/2 \leftrightarrow \pm 1/2$ in state B comprises 30% of the total

resonance intensity of the ^{23}Na in state B. The transition $1/2 \leftrightarrow -1/2$ in state B has a single Larmor frequency ω_L in first order effect, and its integrated resonance intensity is 40% of the total resonance intensity of the ^{23}Na in state B. When the ^{23}Na in state B has a single Larmor frequency ω_L, it has two different T_2.

If the rate of exchange between states A and B is such that $\tau_A \ll T_{2A}$ and $\tau_B \ll T_{2A}$, T'_{2B} (τ_A, the mean lifetime for a stay in state A; T_{2A} and T'_{2B}, the respective T_2 of the ^{23}Na in state A and of the transition $1/2 \leftrightarrow -1/2$ in state B in the absence of exchange), then the transitions $1/2 \leftrightarrow -1/2$ in states A and B are merged into a single transition. Its transverse relaxation time T'_2 is given by the well-known expression:

$$1/T'_2 = p_A/T_{2A} + p_B/T'_{2B}, \tag{1}$$

where p_A and p_B are the fractional populations of the ^{23}Na in states A and B. The normalized line-shape function for this transition at a small rotatory radio-frequency field H_1 is

$$g'(\omega) = \frac{1}{\pi} \frac{T'_2}{1 + T'^2_2(\omega_L - \omega)^2} \qquad (\text{small } H_1). \tag{2}$$

We may put for most tissues and other unoriented systems

$$\int_0^\infty \omega f_\pm(\omega) d\omega = \omega_L. \tag{3}$$

If the rate of exchange between states A and B is such that $\tau_A \ll T_{2A}$, $\tau_B \ll T_{2A}$, T''_{2B}, and $\tau_B^2(\omega_L - \omega)^2 \ll 1$ (T''_{2B}, the T_2 of the transitions $\pm 3/2 \leftrightarrow \pm 1/2$ in state B in the absence of exchange; $T''_{2B} \leq T'_{2B}$), then the transitions $3/2 \leftrightarrow 1/2$ of the ^{23}Na in states A and B are merged into a single line centered at ω_L (see Appendix). Its normalized line-shape function is

$$g''(\omega) = \frac{1}{\pi} \frac{T''_2}{1 + T''^2_2(\omega_L - \omega)^2} \qquad (\text{small } H_1) \tag{4}$$

$$1/T''_2 = p_A/T_{2A} + p_B/T''_{2B} + p_B\tau_B \int_0^\infty (\omega_L - \omega)^2 f_+(\omega) d\omega. \tag{5}$$

Eqs. 4 and 5 are also true for the transition $-3/2 \leftrightarrow -1/2$ because $f_-(\omega)$ must be the mirror mirage of $f_+(\omega)$. The transverse relaxation time T''_2 for the transitions $\pm 3/2 \leftrightarrow \pm 1/2$ of the exchanging nuclei is shorter than T'_2, unless (*i*) τ_B is so small that the last term in Eq. 5 can be neglected (condition IV *b* and not IV *a*) or (*ii*) $\tau_B \ll \tau_c$ (condition IV *a*).

Therefore, under the given conditions, the steady-state resonance of ^{23}Na in tissue or other unoriented systems may be expressed by the normalized function:

$$g(\omega) = 0.4g'(\omega) + 0.6g''(\omega) \qquad (\text{small } H_1). \tag{6}$$

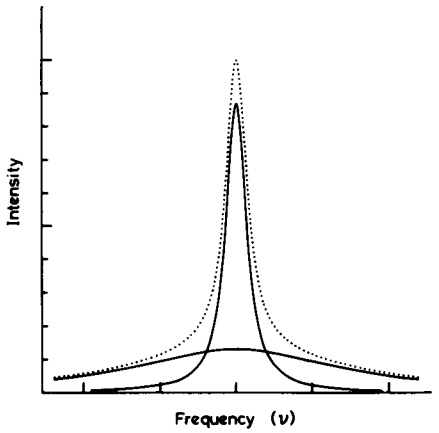

FIGURE 1 Theoretical line shape of steady-state resonance of tissue ^{23}Na (in the case that slow T_2 = 10 ms and fast T_2 = 1 ms). The dotted curve is the total resonance signal. The solid curves indicate its two components, both centered at the same Larmor frequency but characterized by different T_2. The narrow component with longer T_2 represents the transition $1/2 \leftrightarrow -1/2$ and comprises 40% of the total resonance intensity. The broad component represents the transitions $\pm 3/2 \leftrightarrow \pm 1/2$. The scale markers on the abscissa are at intervals of 100 Hz. The resonance intensity is expressed in an arbitrary unit.

It consists of two components, both centered at the same frequency (Fig. 1). The narrower component has the longer relaxation time T_2' and comprises 40% of the total integrated intensity. The broader component has the shorter relaxation time T_2'' and is expected to be scarcely visible in ordinary steady-state NMR spectroscopy when T_2'' is much shorter. The observed steady-state signal and the occurrence of two different T_2 can be thus explained.

If the exchange of ^{23}Na between states A and B is less rapid than defined above, the transitions in states A and B are not completely merged, and the system has more than two different values of T_2. It is doubtful, however, that more than two T_2 can be experimentally distinguished when the difference in T_2 is small.

For oriented systems, Eq. 3 is not valid. The normalized shape function $g(\omega)$ for the ^{23}Na resonance of such systems is, under the given conditions,

$$g(\omega) = 0.4g'(\omega) + 0.3g_+''(\omega) + 0.3g_-''(\omega), \tag{7}$$

$$g_\pm''(\omega) = \frac{1}{\pi} \frac{T_2'''}{1 + T_2'''^2(\omega_{m\pm} - \omega)^2} \qquad (\text{small } H_1), \tag{8}$$

$$1/T_2''' = p_A/T_{2A} + p_B/T_{2B}' + p_B\tau_B \int_0^\infty (\omega_{m+} - \omega)^2 f_+(\omega)d\omega, \tag{9}$$

$$\omega_{m\pm} = p_A\omega_L + p_B \int_0^\infty \omega f_\pm(\omega)d\omega. \tag{10}$$

It consists of three Lorentzian bands, one central band and two satellites on each side

of it. The central band represents the transition $1/2 \leftrightarrow -1/2$, and the satellites, the transitions $\pm 3/2 \leftrightarrow \pm 1/2$. The central band has the longer relaxation time T_2' and accounts for 40% of the total intensity. The satellites have the shorter relaxation time T_2''; they are scarcely visible when T_2'' is so small.

DISCUSSION

According to Edzes et al. (12), the signal of tissue ^{23}Na will consist of three bands, a central band and two satellites on each side of it, and the satellites will be so broad as to be difficult to detect. The present work predicts, however, that all the transitions of ^{23}Na in tissue (or, at least, tissue composed of unoriented cells) will possess the same Larmor frequency.

The theoretical line shape of tissue ^{23}Na submitted in the present paper is consistent with the observation by Czeisler and Swift (15). They revealed, by a high-resolution spectroscopy, the occurrence of a broader signal in the ^{23}Na spectrum of frog muscle; the broader and the readily observable narrower signal are centered at the same frequency. But this agreement between the theoretical and the observed line shape is not decisive, for the integrated resonance intensity has not been measured.

A question arises concerning the validity of the condition of rapid exchange (condition II), for the time of exchange across the cell membrane is clearly far larger than T_2 for ^{23}Na in NaCl solution (57 ms for dilute solution [16]). It should be noted here that in most tissues, the amount of the extracellular Na^+ is comparable to the amount of the intracellular Na^+. One possible explanation is that (*i*) a fraction of extracellular ^{23}Na will interact, in the sense defined by condition IV, with the field gradients at the outer surface of the cell membrane, and (*ii*) this fraction of ^{23}Na will be in appropriately rapid exchange with the remaining extracellular ^{23}Na. In this situation, we have four T_2 (two slow T_2 and two fast T_2). But, if the differences between the slow T_2 and between the fast T_2 are small, only two T_2 can be experimentally distinguished.[1] With this respect, further study is demanded.

APPENDIX

It will be assumed that exchange of nuclei occurs between states I and II. The nuclei in state I have a single Larmor angular frequency ω_I. The nuclei in state II have continuously distributed Larmor frequencies; their normalized line-shape function without dipolar broadening will be denoted by $f(\omega)$. For slow passage and small H_1, the modified Bloch equations for this system are

$$\tau_I^{-1}(1 + \tau_I\alpha_I)G_I - \tau_{II}^{-1}G_{II} = -i\gamma H_1 M_0 p_I, \tag{10}$$

$$-\tau_I^{-1}\sigma G_I + \tau_{II}^{-1}G_{II} = -i\gamma H_1 M_0 p_{II}\sigma, \tag{11}$$

$$\sigma = \int_0^\infty \frac{f(\omega')}{1 + \tau_{II}\alpha_{II}} d\omega', \tag{12}$$

[1] Another possible explanation is that the ^{23}Na nuclei at both surfaces of the cell membrane will exchange their spin energy with each other so rapidly that they are characterized by the same relaxation times.

$$\alpha_I = 1/T_{2I} - i(\omega_I - \omega), \quad \alpha_{II} = 1/T_{2II} - i(\omega' - \omega), \tag{13}$$

$$G_I = u_I + iv_I, \quad G_{II} = u_{II} + iv_{II}, \tag{14}$$

where M_0 is the magnetization along the direction of the applied static magnetic field H_0 in the absence of H_1; γ is the gyromagnetic ratio; p_I and p_{II} are the fractional populations of states I and II; τ_I is the mean lifetime for a stay in state I, and τ_{II}, in state II; T_{2I} and T_{2II} are the T_2 of the nuclei in states I and II in the absence of exchange; u_j and v_j are the transverse components of magnetization along and perpendicular to the direction of H_1. The total complex moment is, therefore, given by

$$G = G_I + G_{II} = -i\gamma H_1 M_0(\tau_I + \tau_{II}) \frac{p_I^2 + p_{II}(1 + p_I + p_{II}\tau_I\alpha_I)\sigma}{1 + \tau_I\alpha_I - \sigma}. \tag{15}$$

For the limiting case that $\tau_I \ll T_{2I}$, $\tau_{II} \ll T_{2I}$, T_{2II}, and $\tau_{II}^2(\omega_1 - \omega)^2 \ll 1$, we obtain

$$G = -i\gamma H_1 M_0(1/[1/T_2^* - i(\omega_m - \omega)]), \tag{16}$$

$$1/T_2^* = p_I/T_{2I} + p_{II}/T_{2II} + p_{II}\tau_{II} \int_0^\infty (\omega_m - \omega)^2 f(\omega)d\omega, \tag{17}$$

$$\omega_m = p_1\omega_I + p_{II} \int_0^\infty \omega f(\omega)d\omega. \tag{18}$$

The absorption signal at small H_1 is proportional to the imaginary part:

$$v = v_I + v_{II} = -\gamma H_1 M_0(T_2^*/[1 + T_2^{*2}(\omega_m - \omega)^2]). \tag{19}$$

If the equation:

$$\int_0^\infty \omega f(\omega)d\omega = \omega_I \tag{20}$$

is valid, Eqs. 17–19 are reduced to

$$v = -\gamma H_1 M_0(T_2^*/[1 + T_2^{*2}(\omega_I - \omega)^2]), \tag{21}$$

$$1/T_2^* = p_I/T_{2I} + p_{II}/T_{2II} + p_{II}\tau_{II} \int_0^\infty (\omega_I - \omega)^2 f(\omega)d\omega. \tag{22}$$

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