The Longitudinal Relaxographic NMR "Shutter-Speed" for Equilibrium Transcytolemmal Water Exchange Varies with Interstitial CR Level

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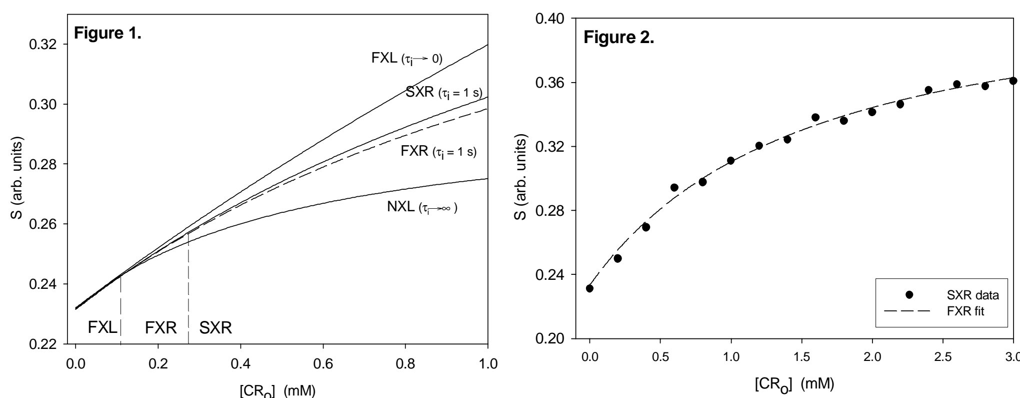
INTRODUCTION: The accurate relationship between contrast reagent concentration, [CR], and the measurable properties of tissue longitudinal ^1H_2O magnetization is crucial for the quantitative analysis of bolus-tracking (B-T) data (dynamic contrast enhancement). For the hyperfine mechanism, water must make molecular contact with CR, but while Gd(III) chelate CRs enter at most the interstitium, most water is intracellular. Thus, the equilibrium transcytolemmal water exchange becomes an issue. It has been shown that as the interstitial CR level increases during a B-T study, the NMR "shutter-speed" for this exchange increases, and the reaction *appears* to slow down (1-4). For most tissues, neglect of this effect leads to significant errors in the calculation of pharmacokinetic parameters. This can be understood in terms of passage through sequential exchange "regimes" as f([CR]) (1). Here, we derive the definitions of these regimes for the case of steady-state longitudinal magnetization such as would be measured with a standard, spoiled gradient-recalled-echo acquisition.

THEORY: The ratio of the measured steady-state signal intensity (S) to its Boltzmann equilibrium value (S_0) is often termed the saturation factor ($\mathbf{S}$), though really an unsaturation factor. The parsimonious two-site-exchange (2SX) situation obtaining for extra- and intracellular ^1H_2O can cause bi-exponential longitudinal relaxation when interstitial CR is present. For $\mathbf{S}$, this is expressed in Equation [1] where: the a factors represent the contributions of the two signals, one with large and one with

$$S/S_0 = \mathbf{S} = a_L \bullet \mathbf{S}_L + a_S \bullet \mathbf{S}_S \quad [1]; \qquad \mathbf{S}_{L,S} = \sin\alpha(1 - E_{1L,S})/(1 - E_{1L,S} \bullet \cos\alpha) \quad [2]$$

small longitudinal relaxation time, T_{1L} and T_{1S}, respectively ($a_L + a_S \equiv 1$). The component saturation factors are given as in Equation [2] where: $E_{1L,S} \equiv \exp(-t_R \bullet R_{1L,S})$, α and t_R are the read pulse flip angle (in degrees) and repetition interval, and the relaxation rate constants, $R_{1L,S} \equiv (T_{1L,S})^{-1}$. The interstitial CR concentration, $[CR_o]$ (o for "outside") dependence enters expressions for the a and R_1 quantities through nonlinear, integral relationships that include 2SX parameters [such as p_o, r_{1o}, and R_{1o0} (interstitial water fraction, CR relaxivity, and rate constant in the absence of exchange and CR), τ_i and R_{1i} (intracellular mean water lifetime and rate constant in the absence of exchange)] and pharmacokinetic parameters [such as K^{trans} (CR extravasation transfer rate constant), h (microvascular hematocrit), and f_W (tissue water volume fraction)] (1-4).

RESULTS: Equation [1] can accommodate any τ_i magnitude. Very large values describe the situation when the exchange reaction is nonexistent or very slow; the *no-exchange-limit* [NXL] or the *slow-exchange-limit* [SXL], respectively. We can simulate the NXL by making τ_i = 1 Ms; the bottom curve in **Figure 1** {S as f($[CR_o]$)}, with also p_o = 0.11, r_{1o} = 3.8 $(mM)^{-1}s^{-1}$, R_{1o0} = 0.55 s^{-1}, R_{1i} = 0.69 s^{-1}, α = 45°, and t_R = 0.2 s. On the other hand, when τ_i is vanishingly small, the reaction is infinitely fast; in the *fast-exchange-limit* [FXL]. The top Fig. 1 curve (FXL) was generated with the same parameters except τ_i = 1 μs. The region between the top and bottom curves represents the sensitivity to exchange kinetics for this particular case – the exchange regime can vary from NXL to FXL. The middle (solid) Fig. 1 curve is calculated with the same parameters except that τ_i is held constant at the physiologically reasonable value of 1.1 s. For reasons that will become clear below, this curve is labeled *slow-exchange-regime* [SXR].



The value of $[CR_o]$ does not affect the exchange kinetics (the τ_i magnitude) (4). However, since it does change the NMR shutter-speed, $|r_{1o}[CR_o] + R_{1o0} - R_{1i}|$, the exchange regime can vary with $[CR_o]$ following a bolus CR injection. This is seen in Fig. 1. When τ_i is vanishingly small, R_{1L} can be substituted with the simple, linear FXL expression $[r_{1o} \bullet p_o \bullet [CR_o] + R_{10}$ (R_{10} is the pre-CR rate constant)], which has no τ_i dependence. But, the value of a_S also vanishes as $[CR_o] \rightarrow 0$ (1), and thus $a_L \approx 1$. Therefore, at very low $[CR_o]$, Eq. [1] is identical to the FXL curve independent of the actual τ_i value. Next, there is a slightly less simplified version of Eq. [1], with a_L = 1 and a_S = 0, but R_{1L} is not replaced with the FXL expression. This represents the *fast-exchange-regime* [FXR] (4). The FXR curve for τ_i = 1.1 s is shown as dashed in Fig. 1. One sees that at very low $[CR_o]$, the FXR (and SXR) curves match the simple FXL curve, and are τ_i–insensitive. Above ~ 110 μM, the FXR and SXR curves depart the FXL curve for this case. The system has entered the FX regime [FXR]. Above ~ 290 μM, the SXR curve departs the FXR curve, and the system has entered the SX regime [SXR]. Because of the shutter-speed increase with $[CR_o]$, the reaction appears to slow down, even though the actual kinetics remain unchanged (here, τ_i = 1.1 s); a tissue property fixed at physiological temperature.

In the analyses of B-T data, the simple FXL relationship had been universally incorporated into pharmacokinetic rate laws. Thus, it had been implicitly assumed that $\tau_i \approx 0$. But, it has been shown that this can cause significant underestimations of K^{trans} and p_o, to say nothing of τ_i, and that constraint to FXL will probably be incorrect for most tissues, CR doses, and field strengths (1-4). Use of the FXR-allowed relationship improves the situation considerably: raising K^{trans} and p_o, and giving realistic τ_i values (4). In a study of rodent tumor B-T data, the additional incorporation of Eq. [1] (SXR) led to further increases in τ_i but not in K^{trans} or p_o (4). This is explained in **Figure 2**. The Fig. 1 SXR curve has been discretized (circles), had (±2%) noise added, and plotted out to 3 mM. These simulated "data" were fitted with the FXR-allowed algorithm (Eq. [1], with a_L = 1 and a_S = 0), with all parameters the same but with variable τ_i. The dashed best-fitted curve in Fig. 2 is seen to agree with the data perfectly. The τ_i value for this fitting is 0.87 s, with an uncertainty (σ) of ±0.8%. Thus, when the system actually sorties from the FXR into the SXR, the use of the FXR-allowed (really FXL/FXR-constrained) analysis underestimates τ_i, by 21% in this case (the τ_i used to construct the data was 1.1 s). In a pharmacokinetic B-T analysis, the τ_i uncertainty will be governed by how long the system spends in the FXR and/or SXR during the bolus passage (4).

DISCUSSION: We have set out the mathematical formalism describing the intermediate exchange regimes for equilibrium transcytolemmal water transport. For a particular set of 2SX and pulse sequence parameters, Fig. 1 shows how the system can undergo a progression of "regime changes" [FXL → FXR → SXR → FXR → FXL] as CR washes in and out of the interstitium. When one considers the noise (Fig. 2) present in experimental data, the "effective" trigger $[CR_o]$ values for these changes become larger. Thus, for many (if not most) tissues *in vivo*, the system may never reach the SXR within experimental error. But, systems often reach their FXRs, and correction for this is important. The tigger $[CR_o]$ values are field-dependent (5).

SUPPORT: NIH (RO1 EB00422, and RO1 NS40801); DOE(DE-AC02-98CH108)

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