Estimating Intracellular Lithium in Brain in Vivo by Lithium-7 MRS

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Introduction: The therapeutic mechanism of action of lithium (Li), an elemental cation used in the treatment of bipolar disorder, is unknown. Lithium is presumed to work intracellularly. While the typical therapeutic serum (and perhaps brain) concentration is 0.6-1.2 mM, the fraction of intracellular Li in the brain *in vivo* is not known. It is not yet possible to determine, directly and noninvasively, the intra-/extracellular distribution of Li in human brain *in vivo*. Reagents exist for separate observation of intra- and extracellular NMR signals in cellular systems *in vitro*, but the blood-brain barrier is impermeable to such shift reagents for *in vivo* studies. Lithium-7 MR is the only technique available for measuring noninvasively the concentration of Li in the brain *in vivo*.[1] We recently reported localized ^{7}Li MRS studies of total Li concentration and spin relaxation in rat brain *in vivo*.[2,3]

For a spin-3/2 nucleus like ^{23}Na in a single compartment, intrinsic biexponential transverse (T_2) spin relaxation is common in biological systems.[4] Although ^{7}Li is also spin-3/2, its spin relaxation is only weakly quadrupolar.[1] Intrinsic biexponential T_2 relaxation has not been clearly observed for ^{7}Li in biological systems.[1] Studies on cellular systems including erythrocytes,[5] neuroblastoma,[6] lymphoblastoma,[6] chromaffin,[7] halotolerant bacteria,[8] and isolated frog heart[9] found monoexponential T_2 behavior intracellularly for ^{7}Li. Because of increased binding and the relatively restricted intracellular environment, cationic T_2 is expected and found to be lower intracellularly than extracellularly.[5,8,10] Assuming the same holds true in the brain *in vivo*, then biexponential behavior in a localized ^{7}Li MRS experiment, if observed, can tentatively be attributed to separate signals from the intra- and extracellular compartments.

We have measured ^{7}Li T_2s *in vivo* in rat brain using localized PRESS.[2] Because these measurements usually suffer from relatively low SNR, particularly at therapeutic concentrations, monoexponential decay was assumed. However, at high Li doses biexponential T_2 behavior can be observed. Here we report measurements of biexponential ^{7}Li T_2 relaxation in rat brain *in vivo,* which we use to estimate the compartmental distribution of Li. Further, we use these biexponential T_2 results as a basis for estimating Li compartmental distribution from previously determined[2] monoexponential T_2 decays using a simple linear approximation.

Methods: Male, Sprague-Dawley rats were dosed IP with LiCl [2.5 meq/kg twice daily for 1-2 weeks (N = 4, taken from the previous study[2]), or 3 doses of 5 meq/kg over 1.5 days (N = 4)]. For the 2.5 meq/kg doses, brain Li was 1.4-2.2 mM; for the 5 meq/kg dose it was estimated as 3-5 mM. Rats for which the T_2 decay was only fit monoexponentially were dosed variously at 1.0 to 2.5 meq/kg as described previously.[2] Localized ^{7}Li T_2s were measured using PRESS or STEAM at 77.7 MHz on a GE Omega CSI spectrometer. Spectral acquisition and localization details were the same or similar to those given previously.[2] For these 8 cases, a biexponential fit using the nonlinear estimation module in Statistica (Statsoft Inc., Tulsa OK) explained substantially more of the variance than the alternative monoexponential fit. For these cases the fit yielded the Li compartmental T_2s and distribution directly (assuming equal ^{7}Li visibilities in both compartments). For the previous cases where the data could only be fit to a monoexponential decay,[2] the intracellular fraction was estimated using the linear interpolation:

$$\% \text{ intracellular} = 100(T_{2e} - T_{2obs})/(T_{2e} - T_{2i})$$

where the averages of the short and long components of the biexponential decays of the 8 cases above were identified as the intracellular (T_{2i}) and extracellular (plus CSF) (T_{2e}) relaxation times, respectively, and T_{2obs} was the observed monoexponential T_2.

Results: For the 8 cases of observed biexponential T_2 behavior, T_{2i} = 15±8 ms, T_{2e} = 147±39 ms, % intracellular = 63±12, % extracellular = 37±12. These T_2 values are in reasonable agreement with those seen in cellular systems.[5-9] The method for estimating % intracellular Li from monoexponential T_2 data was tested on the 8 biexponential cases from the corresponding best monoexponential fits. These results are shown in the Table. There was reasonable agreement (±20%) between the two methods in 7 of the 8 cases. For the previously reported monoexponential relaxation data, the average T_2 = 82±20 ms (N = 16).[2] This yielded % intracellular Li of 49±15. The total range observed previously for T_2 was from 53 to 113 ms,[2] which corresponds to a % intracellular Li of 71 to 26%, respectively.

Rat	monoexp. T_{2obs} (ms)	% intra. (direct biexp.)	% intra. (monoexp. approx.)
1	75	58	55
2	72	64	57
3	113	68	26
4	108	37	30
5	68	66	60
6	49	70	74
7	55	75	70
8	42	64	80
avg	73±26	63±12	56±20

Discussion: This work is the first attempt to estimate the intra-/extracellular distribution of Li in brain *in vivo*. Our work suggests that, unlike Na, a substantial fraction of Li enters the cell. This is not unexpected if the mechanism of action of Li in bipolar disorder is intracellular. The interpolation method for monoexponential decays may provide a rough estimate of intracellular Li when biexponential decay is not observed, as will probably be the case for human studies. However, some estimated intra-/extracellular distributions are close to 60:40, which is the ratio expected for pure intrinsic biexponential T_2 relaxation of spin-3/2 nuclei.[4] A better estimate of T_2 biexponential behavior and confirmation of monoexponential single-compartment spin relaxation in brain *in vivo* are needed. Substantial increases in SNR or different experimental approaches are required to achieve these goals.

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References:

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