Intracellular Lithium by ^{7}Li MRS: Effect of Total Li Concentration in Brain

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Introduction: Lithium (Li) is an elemental cation used in the treatment of bipolar disorder. It is presumed to work intracellularly, but the fraction of intracellular Li in the brain *in vivo* is not known. Shift reagents can separate intracellular and extracellular NMR signals of cellular preparations *in vitro*, but are typically precluded from *in vivo* studies of brain. Lithium-7 MR is the only technique available for noninvasively measuring the concentration of Li in the brain *in vivo*.[1] We have reported localized ^{7}Li MRS studies of total Li concentration and spin relaxation in rat brain *in vivo*.[2-3] At high Li doses, unambiguous biexponential T_2 behavior can be readily observed.[4] Although intrinsic biexponential transverse spin relaxation might be expected for a spin-3/2 nucleus in a biological system, ^{7}Li's spin relaxation is only weakly quadrupolar,[1] and intrinsic biexponential relaxation has not been observed either intracellularly or extracellularly for ^{7}Li in a range of biological systems.[1,4] Assuming the same holds true for the brain *in vivo*, then biexponential behavior in a localized ^{7}Li MRS experiment, if observed, can be attributed to separate signals from the intracellular and extracellular (plus CSF) compartments. The two-compartment (intra-/extracellular) assumption is common in MR studies of brain.[5] Because of increased binding, cationic T_2 is expected to be lower intracellularly than extracellularly.[5] Li^+ binds more strongly to the inner rather than the outer leaflet of the plasma membrane due to the higher concentration of anionic phospholipids in the inner leaflet.[6] In our initial work[4] using this approach, we estimated intracellular Li in rat brain *in vivo* under a variety of MRS and dosing conditions at 4.7 T. Here we report biexponential ^{7}Li T_2 relaxation studies in rat brain at 7 T with isotopically enriched ^{7}LiCl to determine the compartmental distribution of Li as a function of brain Li concentration, and to assess reproducibility and performance of a simple linear approximation to estimate intracellular Li from monoexponential T_2 decay.[4]

Methods: Thirteen rats (212±25 g) were dosed IP with isotopically enriched ^{7}LiCl [4 x 5 (or 3.25-3.5) meq/kg over 2.0 days]. A voxel (0.43-0.47 ml) totally within brain was chosen using ^{1}H axial and sagittal 2D-RARE MR images on a Bruker 7-T Biospec spectrometer. The localized ^{7}Li T_2s were measured using PRESS with TR of 5 s and 12 TE values from 3.75 to 300 ms at 116.7 MHz. Spectral acquisition, localization, and curve-fitting details were essentially identical for all animals. ^{7}Li T_2 decay curves were fit to a biexponential function using the nonlinear estimation module in Statistica (Statsoft Inc., Tulsa OK). A biexponential fit explained substantially more of the statistical variance (97.8±2.4%) than the alternative monoexponential fit (85.6±3.4%). As expected, the % of the variance explained by the biexponential fit correlated with brain Li concentration (r=0.75). The intracellular fraction of Li was also estimated as previously described[4] using the linear interpolation: % intracellular = $100(T_{2e} - T_{2mono})/(T_{2e} - T_{2i})$, where the intracellular (T_{2i}) and extracellular (T_{2e}) relaxation times were averages of the short and long components, respectively, of the biexponential decay, and T_{2mono} is the T_2 determined using a monoexponential fit.

Table

Rat	Brain [Li] (mM)	% intra Li from biexp.	T_{2i} (intra) (ms)	T_{2e} (extra) (ms)	T_{2mono} (mono) (ms)	% intra Li from monoexp
1	6.1	55.6	14.6	261	107	67.2
2	6.0	52.2	15.2	297	133	57.9
3	5.7	58.7	12.6	309	116	63.9
4	4.7	51.3	16.1	268	124	61.1
5	4.6	64.8	22.1	363	90	73.1
6	4.5	37.3	12.6	273	179	41.5
7	4.1	58.3	18.1	302	106	67.5
8	3.8	53.6	13.4	241	109	66.4
9	3.6	53.2	12.7	264	125	60.7
10	3.5	63.0	17.3	450	104	68.2
11	2.6	54.6	20.3	344	132	58.2
12	2.5	54.2	5.2	235	149	52.2
13	1.1	51.8	11.6	234	73	79.4
Avg ±s.d.	4.06 ±1.46	54.5 ±6.7	14.8 ±4.3	295 ±61	119 ±27	62.9 ±9.5

Results: The results are given in the Table. The dosing regimen produced brain Li concentrations ranging from 1.1 to 6.1 mM. The average T_{2i} of 14.8±4.3 ms was similar to our earlier result, whereas the T_{2e} of 295±61 ms was roughly double the earlier result.[4] The intracellular fraction varied from 37.3 to 64.8%. The intracellular fraction of Li determined by biexponential fit did not correlate with brain Li concentration or T_{2i}, although it did correlate with T_{2e} (r=0.57) and T_{2mono} (r=-0.68). Moreover, these results did not differ between groups having high (cases 1-10) and low (cases 11-13) brain Li concentrations. The interpolation method for estimating % intracellular Li from monoexponentially fitted T_2 data was tested on these 13 cases. T_{2mono} varied from 73 to 179 ms. The interpolated results were on average about 16% higher than, and significantly correlated with (r=0.68), the direct biexponential results.

Discussion: This work supports our previous conclusion that, unlike for Na, a substantial fraction of Li enters the cell *in vivo* in brain.[4] This is consistent with an intracellular mechanism of action of Li in bipolar disorder. Interestingly, the intracellular fraction of Li does not depend on the overall concentration of Li in brain, indicating that the cell does not maintain a constant intracellular Li concentration. The interpolation method for a monoexponential fit may provide a semiquantitative estimate of intracellular Li for cases where biexponential decay is not observed. It is necessary to confirm that single-compartment spin relaxation of ^{7}Li is monoexponential in brain *in vivo*, since some intra-/extracellular distributions are close to 60:40, which is the ratio expected for pure intrinsic biexponential T_2 relaxation.[7]

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References:

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