Does Li Displace Intracellular Na in Brain?: An *In Vivo* ^{23}Na MRI Study

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TARGET AUDIENCE: Researchers and physicians interested in applications of MR techniques to psychiatric disorders.

PURPOSE: Bipolar disorder (BPD) is a devastating mental illness afflicting over 2.3 million Americans. Lithium (Li) is an important first-line and widely prescribed treatment for acute mania and relapse prevention in BPD. Despite much research, its mechanism of therapeutic action is still unknown. Over sixty years ago it was noted that sodium (Na) levels in bodily fluids of bipolar patients changed with mood state. Abnormal Na compartmental distribution was later confirmed in depression and mania using isotope dilution techniques.[1] These and other observations led to the proposal that ionic imbalances, possibly arising from abnormalities in the cellular Na pump, Na,K-ATPase, were associated with BPD.[2] A key biochemical prediction of the hypothesis is that intracellular Na in the brain is elevated in BPD. The objective of this application is to identify the effects of Li on intracellular Na in normal rat brain *in vivo* using ^{23}Na MRI.

METHODS: Sodium-23 MRI data were acquired on a Bruker Biospec 7T animal MRI system. See Fig. 1 for scan details. Quantitative and spin-relaxation data were obtained for two rats, one given IP aqueous LiCl (5 meq/kg) and the other IP saline as a control. Proton and ^{23}Na images are shown in Fig. 1. ROIs were drawn for total brain and several regions of higher intensity containing a large fraction of CSF. For the Li-dosed rat, 4 repeat images were acquired at later scan midpoints and intensities measured, as shown in Fig. 2.

RESULTS: For brain parenchyma, ^{23}Na MRI intensity increased by a maximum of 6.78% at 1.4 hrs after Li injection and then fell slightly over the next two hours. Intensity in the CSF-rich regions slowly increased by about 1.9% over the entire period after Li injection (Fig. 2). For saline at a single post-Li time point, the ^{23}Na signal for parenchyma increased by about 1/3 the level for Li at a similar time. For brain parenchyma over all runs, the detected portion (>1.2 ms TE) of the fast T_2 component averaged 3.8±1.2 ms, while the slow component averaged 15.3±3.5 ms. The % (detected) fast component of the biexponential decay (pre-Li, 49%; 0.6 hrs, 33%; 1.4 hrs, 30%; 2.2 hrs, 52%; 3.2 hrs, 21%) fell with time except for the 2.2-hr scan after Li injection.

DISCUSSION: The ^{23}Na signal detected for the net brain ROI is the sum of the intracellular and extracellular compartments, each of which is presumably biexponential. Assuming Na in the intracellular compartment is less mobile than that in the extracellular compartment, it will have shorter T_2s. Some fraction of the rapidly decaying signal will be lost at our minimum TE of 1.19 ms. Because of its shorter T_2s, more will be lost for intracellular than for extracellular Na. As Li enters the cell and displaces Na, a greater fraction of Na will become extracellular and more completely detected (higher effective visibility), causing the total signal to increase. Thus the total detected ^{23}Na signal will not be constant, but will increase temporarily as the fraction of intracellular Na decreases and extracellular Na correspondingly increases. In rat brain the Li concentration peaks at about 1-2 hours after a single dose, and Li substantially enters the cells within that period. With Li influx into the cell after a single bolus injection, we see first an increase and then a decrease in the ^{23}Na signal as Li later leaves the cell and the brain. As expected, ^{23}Na MRI intensity also increases temporarily for the CSF-rich ROIs, but by a substantially smaller amount as Na moves from the extracellular space to the CSF. Concerning our spin relaxation results, the observed ^{23}Na biexponential behavior is some composite of the two compartmental, biexponential signals. As Na moves from the intracellular to the extracellular compartment, the fraction of fast-relaxing component is expected to decrease, as we generally observe. Assuming a 50:50 distribution of Li between the two compartments and a peak total brain concentration of about 2 mM (from our experience), we estimate the intracellular Li concentration at 1.25 mM. Further assuming 10 mM intracellular Na (estimated 0.5 effective MR visibility under our conditions), 140 mM extracellular Na (estimated 1.0 effective MR visibility under our conditions), and a 1:1 displacement of intracellular Na by Li, we predict a ^{23}Na MRI signal increase of about 4.7%. Given the assumptions, this compares favorably with the 6.8 % maximum detected increase. Saline generates a much reduced ^{23}Na MRI response.

CONCLUSION: Lithium acutely displaces intracellular Na in normal rat brain, supporting the idea that Li's mechanism of therapeutic action in BPD involves normalization of elevated intracellular Na levels arising from defective ionic homeostasis.

REFERENCES:

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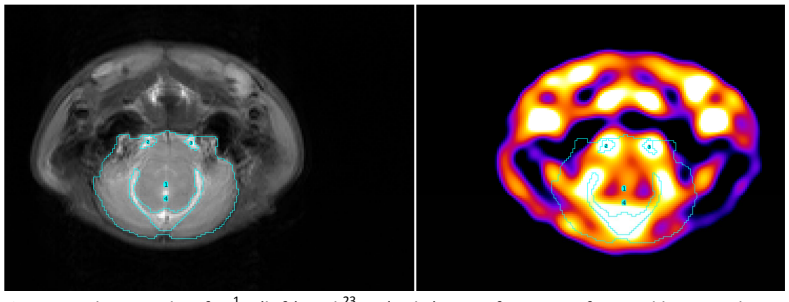

Fig. 1. Axial 6-mm slice for ^{1}H (left) and ^{23}Na (right) MRI of rat. ROIs for total brain and several CSF-rich regions are shown. ^{1}H: RARE, 6 mm slice, FOV 58.8 mm, matrix 256x256, TE 45 ms, TR 3220 ms, 2 averages. ^{23}Na: Gradient echo, 6 mm slice, FOV 58.8 mm, matrix 32 x 32, TE 1.19 ms, TR 100 ms, 900 averages.

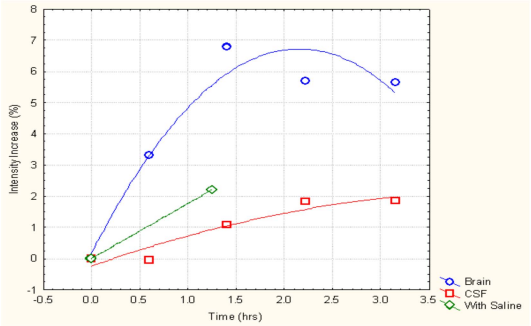

Fig. 2. Plots of ^{23}Na MRI intensity vs. time after bolus IP injection of aq. LiCl (5 meq/kg) for brain and CSF, and after bolus saline.