Quantative Mapping of Lithium in Rat Brain at Therapeutic Doses by Spectroscopic Imaging

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Introduction

Since the discovery that lithium (Li) is efficacious for the treatment of manic depressive illness, there has been active research in the area of brain Li distribution of mammalian systems treated with lithium. However, the relationship of lithium in different brain regions to its function remains largely unknown. Both the therapeutic and neurotoxic side effects of Li are centered mainly in the central nervous system and hence there is considerable interest in understanding the extent of lithium penetration into the central nervous system. The mechanism by which neurotoxic side effects are generated is not known and may, in part, be related to the particular distribution of lithium in the brain. Knowledge of Li distribution in the brain is necessary to localize its action in the brain. The regional specificity in lithium's brain distribution could underlie important steps on its action. Brain levels are now known to show better correlation with clinical efficacy than the plasma values and hence a direct nondestructive measurement of Li in the brain is desirable. Since magnetic resonance technique can be used to observe Li (1-4), it can be an appropriate way to monitor and map the distribution Li in the brain. Earlier studies on animal models at lower field strengths made use of the spin-echo technique (1,2) to image lithium in brain at high dose of Li administration. The feasibility studies on patients under Li therapy at a coarse resolution at 1.5T (3,4) have pointed to the need for higher spatial resolution and better signal to noise ratio. Here we demonstrate the feasibility of quantative spectroscopic imaging of Li in rat brain subvolumes under therapeutic doses.

Methods

***Animal preparation*:** Male Sprague Dawley rats weighing 200-300 g were housed under controlled lighting and temperature. Food and tap water were available ad libitum. The Li protocol consisted of two doses of 2 meq LiCl on the 1st and 2nd day followed by a single 2 meq dose on the morning of the third day. MR imaging studies were done 2-4 hours following the final dose. The above Li dosing leads to serum levels comparable to human therapy.

In vitro Brain Li Measures: A similar group of rats (n=7) was treated at 2meq dose and plasma lithium was measured 8hrs after last injection. The brains were immediately removed and later analyzed by VG ICP- mass spectrometer at the chemical analysis laboratory in Athens, Georgia.

Magnetic Resonance Imaging: All MR studies were performed on a Bruker 7T animal imager operating at 300.0 MHz for ^{1}H and 116.6 MHz for ^{7}Li nucleus. The MR studies were performed using a dual tuned ^{1}H-^{7}Li Litz RF Coil. The ^{1}H scout images were acquired using a spin echo technique with a TE of 20 ms. The Lithium Spectroscopic images were collected as FIDs using the 2DSI technique on the 7 Tesla system. The acquisition parameters were: TR of 0.8s; Number of acquisitions 100; slice thickness 10mm; Fov of 50mm. The acquisition matrix was 8x8 in size.

***Data Analysis*:** All image processing and analysis were performed on a Silicon graphics work station using the Bruker Paravision software (version 2.1.1). The raw spectroscopic imaging data was apodized with a 30Hz line broadening in the time domain.

Results and Discussion

The spectroscopic image data, obtained using protocol 2, was zero filled once in the two spatial dimensions and the final image is shown in Figure1a. In order to analyze the spatial variation of Li, spectra from each voxel was processed in the absolute phase mode and the signal intensity was compared with a signal from a corresponding voxel from a phantom of known Li concentration. The quatitative Li concentration map is shown in Figure 1b. The line widths at half height and the signal to noise for each signal in the voxel were also determined. Those signals with SNR of greater than 6.0 were selected for the purpose of quantitation. The line widths varied by a factor of 2-3 folds across the brain indicating different environment for Li.

Figure 1a

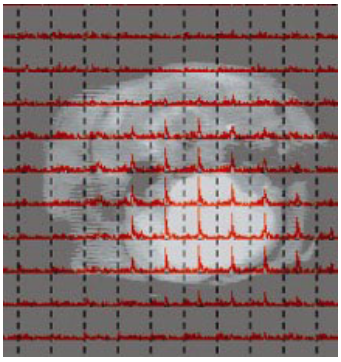

Figure 1b

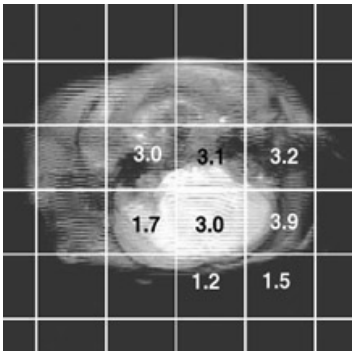

Figure1: a) An axial spectroscopic image of Li with one zero filling in both the spatial dimensions overlaid on ^{1}H image of the rat head b) Li concentrations (in meq) in different voxels of the brain and head tissue.

Conclusions

The brain lithium spectroscopic image can be generated on the 7 tesla imager at therapeutic dose of lithium. The MR derived brain lithium concentrations are in close agreement with those obtained from VG ICP- mass spectrometry method.

Acknowledgements

This research was supported in part by National Alliance for Research in Schizophrenia and Depression (NARSAD).

References

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