Magnetic resonance spectroscopic imaging studies of lithium

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1. Introduction

Lithium (Li) is a naturally occurring alkali metal and is present in humans in only trace amounts [1]. Humans ingest Li from a variety of dietary sources such as drinking water, minerals, plant, and animal tissues [2]. Blood serum concentration in normal humans ranges from 0.16 to 8.6 μM/L. Following the discovery by Cade that Li has an anti manic and a prophylactic effect on bipolar illness [3], Li has been used in the treatment of manic and depressive episodes. The current evidence suggests that Li should be the first choice in the prophylactic treatment of most bipolar patients [4]. Because it is toxic over a certain dose, the blood Li is maintained in a narrow range (0.5–1.2 meq/L) which is

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considered therapeutic. The mechanism of action and how it functions in the brain are largely unknown. It has been suggested that the intracellular $\text{Li}^+$ levels and the intra to extra cellular ratio (I/E) for Li provide useful clinical information in the management of lithium treatment [5].

Since Li is a centrally acting drug, its penetration and distribution in different volumes of the brain have obvious relevance. Lithium is now known to increase the expression of cytoprotective protein Bcl-2 and may exert neuroprotective effects against diverse insults. Current clinical data appear to support the hypothesis that the therapeutic action of lithium may, in part, be responsible for its neuroprotective effects [6]. Chronic administration of lithium significantly increases gray matter content in a regionally selective manner, suggesting a reversal of illness-related atrophy and an increase in the neutrophil volume [7]. Brain levels are now known to show a better correlation with clinical efficacy than the plasma values. For many acutely manic patients, combinations of medications are often crucial to bring symptoms under control. In particular, antidepresants and anti-psychotics may improve response when added to Li.

The development of an appropriate technology to study the brain Li in a noninvasive manner is valuable both in the research and clinical setting. Quantitation of lithium in brain regions, where its action will lead to normalization of the symptoms of the illness, may shed light on the elusive nature of bipolar illness. Although high field magnets will yield a higher signal-to-ratio (SNR), which is a significant advantage when working with a less sensitive nucleus such as lithium the accompanying changes in relaxation of the nucleus may affect the SNR of images and spectra. Thus a realistic measure of the increase in the magnitude of the achievable SNR at high magnetic fields in a mammalian model is necessary.

1.1. Lithium measurements in tissue—current status

Unlike plasma lithium measurements, the tissue and brain lithium studies using the time honored technique such as the atomic absorption (AA) method requires sacrificing the animal. Thus the method can be applied to animal models or on post mortem studies of human brain. Most of the earlier lithium studies in animal models and post mortem brains have used AA technology.

The distribution of lithium in the brain is of importance in lithium therapy and in localizing the action of lithium in the brain. Both the therapeutic and neurotoxic side effects of lithium are centered mainly in 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. The regional specificity of the distribution of Li in the brain could underlie important steps on its action. As $^7\text{Li}$ MR technology will become clinically relevant, adequate new improvements and advances are necessary.

1.2. Tissue lithium measurements by AA and $\alpha$-neutronography methods

Li is not metabolized in the organism and can be determined quantitatively in various tissues. Sprites [8] investigated the distribution of lithium in monkey brain after chronic oral dosing. The average total brain level was 0.5 meq (milli equivalent/kg), the plasma level was 1 meq/l and variable concentrations were found in 32 examined areas of the brain. The regions with highest lithium levels were the anterior thalamus (0.82 meq/kg) followed by the caudate nucleus (0.65 meq/kg). The lowest values were found in the spinal cord, cerebellum, temporal lobe and optic chiasm (all slightly less than 0.4 meq/kg).

The first report of lithium distribution in human brains was based on two cases that had received lithium for 3 and 4 days prior to death and showed an elevated level of lithium in the pons [9]. The highest concentration was in basal ganglia and the pituitary and the lowest in the spinal cord. Another study of brain lithium in humans was reported by Sprites and showed higher concentrations in hypothalamus and white matter compared to cerebral hemispheres, cerebellum, thalamus, and grey matter [8]. As these studies were on post mortem brains, the amount of lithium could be estimated via AA methodology.

In animal model systems, a number of studies have been performed to obtain brain lithium distribution. A large majority of them have studied lithium distribution in rats using AA methodology and some studies have used $\alpha$-Neutronography to obtain lithium density in different histological sections of the brain and other organs. Studies of lithium distribution in rat brains using the AA technique showed lithium to be unevenly distributed in the brain. Lithium characterization in brain tissue has been done in animal studies in post-mortem brains [10–17] after single dose administration of lithium. The earlier chronic administration of lithium suggested a more uniform distribution [11,15]. However, later studies have shown a region specific distribution of lithium [18] with a higher level in the hypothalamus and in the neocortex and the putamen. The study by Nelson et al. [19] via neutronography indicated intermediate levels in thalamus, hypothalamus, septal nuclei, dentategyrus, hippocampus, and substantia grisea centralis. More recently, lithium studies in brain regions and synaptosomes have been performed on a rat model by using graphite furnace atomic absorption spectrophotometry [20]. The results from these determinations show that lithium is heterogeneous distributed among rat brain regions 24 h after a single dose administration of 10 meq/kg LiCl. The brain regions such as hypothalamus, corpus striatum and mid brain were the regions with highest lithium accumulation.

The methods described above are of destructive nature and hence cannot be utilized to measure brain lithium of patients under therapy. Magnetic resonance (MR) techniques on the other hand do not involve any ionizing
radiation and can be performed in a noninvasive manner. Since the early developments, MR has grown into a technique of immense value in radiological and medical applications. The early developmental work in spectroscopic imaging [21] concentrated on studies using the \(^1\)H nucleus. Subsequently, work involving lithium, phosphorus etc. have clearly demonstrated that spectroscopic imaging at moderately high fields is a powerful technique for imaging these nonhydrogen nuclei. Studies on many nuclei of interest in medicine and biology are still at the beginning stage and a brief discussion of the same is given below.

2. MR studies on nuclei of biological interest

Developments of MR methodologies and, in particular, MRSI of nonhydrogen nuclei have been limited due to their low signal to noise ratios (SNRs) compared to that obtainable from protons. Lithium (\(^7\)Li) is a relatively new addition to the developments and applications of new MR technologies such as MRSI. Motivation for the developments of MR technology involving lithium arises from the fact that information about the distribution and properties of lithium in the microenvironment of the brain is important for understanding brain function. The magnetic properties such as the magnetogyric ratio (\(\gamma\)), and the relative sensitivity of the nuclei are listed in Table 1. Among the several low-gamma nuclei listed in the Table, \(^7\)Li nucleus has the highest MR sensitivity. Its moderate sensitivity together with its high natural abundance has made it an attractive nucleus for MR studies.

3. Types of RF coils used

Coils of different size and shape have been used that meet the requirements of a particular study. These coils can be mainly classified into surface and volume coils. In many lithium studies investigators have used single loop surface coils [22–25]. Two coil assemblies consisting of surface or volume coils [26–28] and more recently double tuned volume coils such as Linear Litz coils [29,30] have been used. Attaining a high sensitivity from RF coils requires optimization of several of the parameters shown in the equation below [31]:

\[
\text{SNR} = \frac{\rho_0 N \gamma h^2}{4 k_B T_{\text{sample}}} \sqrt{\frac{\mu_0 Q}{4 k_B T_{\text{eff}}(BW)V_{\text{coil}}}}
\]

where \(V_{\text{coil}}\) is the coil volume, \(Q\) is the quality factor of the coil, \(k_B\) is the Boltzman constant, \(BW\) is the receiver band width, and \(T_{\text{sample}}\) is the temperature of the subject being studied (generally in the neighborhood of 310 °K). \(T_{\text{eff}}\) characterizes the total noise temperature which arises from contributions consisting of resistive losses from the coil, the subject under study, and the preamplifier unit employed in the study (\(T_{\text{amp}}\)). Thus for a given sample, a reduction in coil volume (\(V_{\text{coil}}\)) and minimizing \(T_{\text{eff}}\) will lead to increased sensitivity.

The volume coils provide a better homogeneity than surface coils and hence have been used in most of the recent studies. Recent studies on mammalian model systems at higher field strengths have used more advanced coil systems to obtain a higher signal to noise ratio [29].

4. Relaxation times of \(^7\)Li in solution and in vivo systems

Naturally occurring Li consists of the \(^7\)Li and \(^6\)Li isotopes at 92.6 and 7.4% abundances, respectively [32]. Both the isotopes are quadrupolar. The interaction of nuclear quadrupole and the electric field gradient arising from the local electronic environment provides the dominant relaxation mechanism for the spin states. In the in vivo situation, the \(T_1\) values are in the range of 2–3 s while the values of \(T_2\) are in the range of 20–30 ms at 7 T. Lithium-7 (\(I = 3/2\)) is the isotope of choice for most studies because of its higher natural isotopic abundance, higher magnetic moment and its more favorable relaxation properties compared with \(^6\)Li (\(I = 1\)).

A study of relaxation properties in different brain regions can provide an indication of the environment of the lithium in the brain tissue. The different properties of lithium in the microenvironment can shed more light on its function. Knowledge of the relaxation times of \(^7\)Li is also necessary in the entire process of optimization of MR experiments. Table 2 lists the relaxation times at different field strengths on some animal models. As can be seen from the table, both \(T_1\) and \(T_2\) in the puppy head exhibited biexponential decay. The studies on rat head (non-localized) and brain (localized) indicate biexponential decay. The \(T_1\) exhibited a

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Spin (I)</th>
<th>Natural abundance (%)</th>
<th>Magnetogyric ratio ((\times 10^3)) (rad T(^{-1}) s(^{-1}))</th>
<th>Sensitivity</th>
<th>MHz at 7.0 T</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H</td>
<td>(1/2)</td>
<td>99.985</td>
<td>26.7510</td>
<td>1.00</td>
<td>300</td>
</tr>
<tr>
<td>(^7)Li</td>
<td>(3/2)</td>
<td>92.4</td>
<td>10.3964</td>
<td>0.29</td>
<td>116.7</td>
</tr>
<tr>
<td>(^{13})C</td>
<td>(1/2)</td>
<td>1.10</td>
<td>6.7263</td>
<td>0.0159</td>
<td>75.432</td>
</tr>
<tr>
<td>(^{23})Na</td>
<td>(3/2)</td>
<td>100</td>
<td>7.0761</td>
<td>0.0925</td>
<td>79.353</td>
</tr>
<tr>
<td>(^{31})P</td>
<td>(1/2)</td>
<td>100</td>
<td>10.8289</td>
<td>0.0663</td>
<td>121.443</td>
</tr>
</tbody>
</table>

Table 1

Properties of \(^7\)Li and other low gamma nuclei in comparison with the \(^1\)H nucleus

\[6^\text{Li} \quad \frac{g}{h} = \frac{6\cdot10^{-27} \text{J}}{13 \text{eV}} \quad \text{magnetic moment and its more favorable relaxation properties compared with } 6^\text{Li} \quad \frac{g}{h} = \frac{6\cdot10^{-27} \text{J}}{13 \text{eV}} \quad \text{magnetic moment and its more favorable relaxation properties compared with } 6^\text{Li} \]
monoeXponential decay. Measurements on the rat head at 7 T indicated monoeXponential decay curves for both \( T_1 \) and \( T_2 \) relaxation times. The small \( T_2 \) value suggests that the spectroscopic or imaging experiment should minimize losses from \( T_2 \) decay before data acquisition begins.

The available in vivo MR studies have indicated a substantial increase in signal intensity of \( ^7 \)Li nucleus in going from 2.2 to 7 T. Our ability to obtain signal from small brain voxels such as \( \sim 0.1 \) ml in about 60 min indicates a significant step in the study of brain regions. In addition to the improvements due to high field strength MR imagers, there are more ways of increasing the signal to noise as discussed below. The animals will be dosed using enriched LiCl leading to \( \sim 8\% \) increase in SNR. One can obtain significant increase by a factor of 3.65 by using a shorter brain only coil, a possible increase of 41% due to quadrature coil, and a modest 36% increase via incorporation of the heteronuclear NOE technique to the SI experiment. This results in a seven-fold increase (compounded) in intensity over earlier published studies.

5. Magnetic resonance (MR) imaging and spectroscopic studies of lithium

Renshaw and co-workers [33–35] were the first to report in vivo \( ^7 \)Li MR images in animal models. In one study, [33] they reported a low resolution (1 \( \times \) 4 \( \times \) 40 mm\(^3\)) \( ^7 \)Li image of the abdomen of a (dead) rat, which had received two intra-peritoneal injections of 10 mmol/kg LiCl separated by 24 h. The \( ^7 \)Li image was acquired over 4 h on a home built 2.2 T instrument using a double tuned \( ^7 \)Li/\( ^1 \)H radio frequency coil. In a second study, Renshaw et al. [34] reported the \( ^7 \)Li image from the head of a puppy treated with a daily dose of 2.4 meq over 3 days. Because a larger animal was used, poorer resolution (1.2 \( \times \) 1.2 \( \times \) 4 cm\(^3\)) could be tolerated in the image. No anatomic detail was seen in the image even with a corresponding proton image. Subsequently we have been able to study by spectroscopic and imaging techniques the rat animal model under various single and multiple dose protocols. The work was performed using an animal imager operating at 4.7 T [27]. For these studies we employed a home built two coil \( ^7 \)Li (inner)/\( ^1 \)H(outer) birdcage design to optimize sensitivity for \( ^7 \)Li independent of \( ^1 \)H. The spin echo \( ^7 \)Li images of the rat head could be obtained in 2–4 h of data acquisition on rats given two 2 mmol/kg doses of LiCl on the first day, two 5 mmol/kg doses on the second day, and a final dose of 10 mmol/kg on the third day. The sagittal view showed basic head and neck and some anatomical details such as the spinal cord and the nasal cavity. It was possible to observe the correlation with different brain regions. At the doses used in this preliminary development study, there was clear indication of the uneven distribution of Li in the brain. The results from five independent studies [36] showed that the distribution was not even with the standardized effect sizes (defined as the ratio of the mean difference to the standard deviation of the differences) as follows: (a) hind to front was 1.71, (b) hind to mid was 2.47 and mid to front was 0.80.

Although variations in lithium concentrations by a factor of two or more are sometimes seen among different brain regions, many of the results are conflicting, possibly owing to ion redistribution at death and/or during sample preparation. MR measurements, on the other hand, can provide information on distribution of lithium in the living tissue in a completely noninvasive way. When there is a change in the lithium in the intra and extra cellular compartments, one can expect the MR \( ^7 \)Li relaxation (\( T_2 \) relaxation) parameter to show variations. Variations in \( T_1 \) and \( T_2 \) can help us to understand changes in intra- to extra cellular ratio [37]. For example, a decrease in the \( T_2 \) value can be interpreted as an increase in the intracellular level. This can be further explored by analyzing the biexponential nature of the \( T_2 \) relaxation decay that can be observed at appropriate field strengths. We have verified this on blood samples drawn from animals treated with different lithium doses [38]. However the relaxation behavior of \( ^7 \)Li is dependent upon the local viscosity and the field strength at which the experiments are performed. The ability to discriminate two pools of lithium in blood samples and possibly in the tissue at lower field strength such as 4.7 T does not appear possible at 7 T.

Subsequent to our studies at 4.7 T, we have studied the rat brain using a higher field instrument such as a 7 T in vivo imager. The preliminary studies indicate that \( ^7 \)Li brain images can be obtained using spectroscopic imaging (SI) technique at therapeutic lithium doses. The plasma levels measured at the end of 8 h post drug administration showed these values to be within the therapeutic window. The images were accumulated in about 1 h, a significant reduction in time compared to studies at 4.7 T. The advantages of moving to higher field are quite evident in
studies such as this. Subsequently we have been able to study the rat animal model under various single and multiple dose protocols by spectroscopic and imaging techniques. Overall there have been steady developments in magnetic resonance spectroscopy and imaging that have made possible the noninvasive measurements of brain lithium concentrations in mammalian subjects [39–42].

The pharmacokinetics of lithium and its concentration in human brain and muscle have been studied by using clinical MRI systems [35,23,43,44]. Following the administration of both single and multiple doses of Lithium carbonate to normal volunteers the in vivo measurement of lithium in the brain was performed in a noninvasive manner using the $^7$Li spectroscopic technique. The earliest in vivo studies of $^7$Li utilized the highly nonuniform excitation field of a surface coil to achieve a crude localization to a region of head and brain [35,23,43]. Attempts to achieve localization via DRESS and ISIS methods have demonstrated the utility of these techniques in obtaining spectra from localized brain volumes. The studies by Gonzalez et al. [45] using the ISIS technique further confirmed the variation of brain lithium of patients with similar lithium concentrations. They have shown on a 1.5 T commercial instrument the feasibility of performing SI studies. These results are similar to those done by Komoroski et al., on a 1.5 T instrument [23]. However the spatial resolution is not sufficient to perform detailed analysis on 1.5 T instruments. Although a single study of chemical shift imaging has been reported [46] there are no further studies on the distribution of lithium in the brain either by spin echo imaging or similar techniques. Recently the methodology for two-dimensional Li-7 imaging on clinical systems has been presented and the feasibility of obtaining spectroscopic imaging (SI) data in vivo state in a clinical scanner has been demonstrated [47]. The signal to noise ratio achieved was sufficient to make valid clinical conclusions on the distribution of brain Li. A clinical interpretation of the data showing the relative concentration as a metabolic image involving the distribution of lithium is more understandable and may help the physician in making quick and valid treatment decisions.

$^7$Li is a quadrupolar nucleus but with a substantial contribution to relaxation via the hetero nuclear dipolar mechanism [48]. Hence, enhancement of the Li signal using the nuclear Overhauser effect (NOE) via the saturation of water resonance is possible (Ramaprasad, unpublished results). This method has not been implemented in spectroscopic or imaging studies of lithium. Developing and implementing new schemes, their implementation on the 7 T system, and further optimization of such studies on test subjects (animals) will be the significant thrust of future studies in our laboratory.

A number of studies have been performed on mammalian models that have yielded a wealth of information on the distribution of lithium in blood tissue and the brain. To date there have been more studies done on rats than on other animals. Magnetic resonance studies have been performed on rats since high field instruments have a small bore size and cannot accommodate bigger animals. Rats are more suitable than mice for MR studies because of their significantly large brain mass. Since lithium has been well characterized in rat models it is a well suited animal model for detailed lithium studies using modern high field animal imagers.

6. Studies using isotopically enriched lithium

Enhanced lithium images of rat brain have been obtained and analyzed earlier [36,49] at 4.7 T. Images from slices at 4 mm thickness were obtained using both $^7$Li at natural abundance (92.6% $^7$Li) and enriched (100% $^7$Li). The obtainable SNR increased by ~7.4% and this also resulted in reduction in data accumulation time of approximately 15%. It can be expected that lithium enriched in $^7$Li will be used in future studies to increase the image quality.

7. Localization techniques applied to $^7$Li nucleus

The various localization techniques that have been used to study the properties of Lithium in localized tissue regions of the head and brain have employed single voxel techniques such as STEAM [27] and PRESS [30]. More recently multivoxel techniques have been used [29] to obtain information from a number of voxels in a single study. Further discussion of these is provided below.

7.1. Single voxel techniques

We will first discuss the results available on lithium properties using localized spectroscopy and provide the motivation for developing SI methods for measuring in vivo lithium for various brain regions in a single set up. The various studies performed to obtain data on lithium properties in localized volumes of interest include methods such as DRESS, STEAM, PRESS, and SI. These studies have been performed to obtain lithium concentrations, lithium pharmacokinetics and lithium diffusion values in voxel(s) of interest. Spectroscopic imaging has an important advantage over single voxel methods in that the signal is collected from a large volume in every data acquisition, and later decoded into many smaller voxels. As such, it provides much more information per unit time than the single voxel methods and thus provides a tool for studying a number of regions in a time frame similar to that used in a single voxel study.

7.2. Brain pharmacokinetics

Lithium pharmacokinetic studies by MR have been performed both using a single voxel technique on the whole brain and by the spectroscopic imaging technique to obtain
7.2.1. Brain pharmacokinetics of lithium by single voxel localization

The pharmacokinetics of lithium uptake and elimination has been measured using the well-known STEAM localized spectroscopy [28]. In this study the uptake of Li into the rat brain was studied by collecting a series of spectra over a period of 22 h. A representative PK profile of the rat brain is shown in Fig. 1. The mean time constant was $\tau_{\text{72 min}}$ and is comparable to values obtained for rat head using a surface coil.

7.3. Localized $^7$Li diffusion studies

A knowledge of brain lithium concentration and its distribution in the brain and its properties in the microenvironment should be useful towards understanding the function of lithium. In vivo MR studies can now provide information on lithium properties in the microenvironment of the brain. These include relaxation times ($T_1$ and $T_2$), local concentrations in the region of interest, and diffusion of the ion in the tissue. The diffusion properties of lithium in the head and brain tissue was first measured using the diffusion sensitized stimulated echo acquisition mode (STEAM) technique. The value of the diffusion coefficient was measured as $0.25 \pm 0.05$ m$^2$/s. Measurements performed along x, y and z directions did not show any anisotropy. The use of SI methodology to further determine diffusion properties in various anatomical regions will be a valuable tool towards attaining these goals.

7.4. Multivoxel technique—spectroscopic imaging (SI)

Spectroscopic MR imaging are techniques for producing spatially resolved MR spectra in a manner analogous to MR imaging. Spatial information is encoded by the application of phase encoding, but in contrast to MR imaging, the read out gradients are omitted to preserve the chemical shift information. The term spectroscopic imaging is applied to procedures that employ the above techniques irrespective of whether the information is finally presented in the form of images or as arrays of conventional spectra. When necessary the number of spatial dimensions from 1 to 3 can be encoded in the protocol depending upon the combinations of phase-encoding gradients used. In further implementations, these methods can be applied in combination with single voxel localization techniques such as STEAM or PRESS. One example might be the use of the PRESS sequence to define a rectangular voxel well within the brain and then to subdivide it into smaller voxels by the phase encoded SI technique.

7.4.1. Case for spectroscopic imaging of $^7$Li

Earlier studies on animal models have made use of the spin-echo technique [30,31] to image the brain lithium. In the spin echo imaging technique, as the echo is generated following a spin excitation, there will be a gradual loss of signal due to $T_2$ decay processes during the echo time which is defined as

$$S = S_0 \exp(-\text{TE}/T_2)$$

where $S_0$ is the intensity following excitation, and TE is the echo time. The signal during the TE time will be negligible when $T_2$ is long compared to TE (as for example at 2.2 and 4.7 T). However, when $T_2$ is small such as at 7 T ($\approx 20$ ms) there can be significant signal loss before acquisition starts. Our attempts to obtain spin echo images at 7 T (using echo times of 6.4 ms) did not yield usable images in the animal model. The conventional SI technique involves exciting the spin system, phase encoding the resultant transverse magnetization with brief field gradients pulses and then reading the signal in the absence of applied field gradients [51]. The pulse sequence that is generally employed in such studies is shown in Fig. 2. Signal losses of the type seen in the spin echo technique will be negligible while using this method.

Fig. 1. Localized pharmacokinetics of lithium in rat brain. The solid curve is the single-exponential fit to the data. Reprinted with permission from Ref. [35].

Fig. 2. SI pulse sequence with phase encoding in the two spatial dimensions for studying the $^7$Li signal distribution along 2 dimensions of a given slice.
technique. Thus, SI is a more powerful tool for studying lithium in different brain regions at this field strength. The SI data at therapeutic doses are obtainable in less than 2 h scan time. Spectroscopic imaging has an important advantage over single voxel methods in that signal is collected from a large volume in every data acquisition, and later decoded into many smaller voxels.

The optimization of the study should address the elimination or reduction of signals from the surrounding tissue that contaminate the brain signal. Theses studies are most necessary when the influence of the signal from extra cranial signal causes distortion of the signal intensities and hence errors in quantitation. The presence of larger signals in the head tissue compared to the brain signals is evident from the imaging studies when lithium is administered at or above 3 meq/kg doses (given twice daily) and generally small at lower doses of lithium. The reasons for this significant shift in the distribution pattern of lithium is not known but it has a positive effect on our study in that we should be able to assess lithium in the brain with better precision at lower doses that lead to therapeutic lithium concentrations (0.5–1.2 meq).

The brain can be studied on high field instruments in controlled conditions to yield highly reproducible results. Improved pulse sequences for rapid clinical applications can then be developed based on our experience with the animal model.

7.4.2. SI Studies on rat thigh muscle

Spectroscopic imaging studies on rat thigh muscle were the first on an animal model using the magnetic resonance technique. These SI studies on the model were performed on the thigh muscle regions at 4.7 T [26]. A home built two-coil assembly that consisting of a 3 cm diameter single turn coil and a figure—eight-shaped loop for the 1H nucleus was used for this purpose [26]. The map of lithium in the active volume of the coil in different segments of the thigh muscle can be seen (Fig. 3). In this image nine voxels (640 µL) showed significant lithium signals. The SI method thus allows the observation of lithium signals from different regions of the thigh muscle (see Fig. 3). Further studies to see the changes in the tissue lithium with a co-administered drug and to separate the intra and extracellular lithium are being pursued in our laboratory. A single 10 meq LiCl was administered as an IP dose and SI data collected 2 h after the injection.

7.4.3. Brain lithium distribution by spectroscopic imaging

Spectroscopic images on rat brains were obtained at various administered doses of lithium. The axial 7Li SI spectral data were obtained under a protocol that used a two 2 meq dose the first day followed by two 5 meq doses the second day and a final single 10 meq dose on the third day and prior to acquiring the spectroscopic images. The cumulative lithium dose was 24 meq and the SI data was record in ~6 min. The results shown in Fig. 4 provide the spectroscopic representation of lithium distribution in the brain and surrounding tissue. An examination of the Lithium intensity in the brain regions indicates nonuniform distribution. A detailed analysis of the signal intensities via integral values for the signals from each voxel showed a variation by a factor of 2. The measured line widths across the brain also indicate variations that reflect different environments for the brain Li that may lead to different functional properties in brain regions.

With the main goal of testing the feasibility of recording the 7Li spectroscopic images at the therapeutic Lithium levels, the Lithium dose was decreased in a stepwise manner. SI data corresponding to each one of the reductions in lithium dose were recorded. A set of spectroscopic and image representation of axial SI data obtained on the rat head under lithium administration according to a different

Fig. 3. A 7Li spectroscopic imaging data from the rat hind limb overlaid on the axial proton image. Reproduced with permission from Ref. [26].

Fig. 4. A 7Li SI spectra recorded using protocol 1. The cumulative dose was 24 meq. Total acquisition time was approximately 6 min.(reprinted with permission from Ref. [29].)
protocol that used 2 meq/kg dose of LiCl twice daily over two days are shown in Fig. 5A and B.

At the administered dose of 3 meq over two days, considerable lithium in the head tissue surrounding the brain was observed. When the dose of lithium administered was decreased to 2 meq/kg, useful SI data could be obtained in 85 min. The $^7$Li data superimposed on $^1$H axial image of the slice is displayed in Fig. 5A. The SI data is represented after one zero filling in each of the two spatial dimensions prior to Fourier Transformation. The results demonstrate a fairly even distribution of lithium in the brain. Interestingly the lithium present in the head tissue is significantly less with many tissue voxel in the head exhibiting no lithium. Based on the serum values obtained at the end of 8 h post last lithium administration, the lithium concentrations are found to be within the therapeutic range.

In order to analyze the spatial variation of lithium, 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 lithium concentration. The quantitative lithium concentration map is shown in Fig. 5B. The MR derived brain lithium concentration in the slice examined was found to be similar to those obtained by VG ICP-mass spectrometry method on rat whole brain.

8. Pharmacokinetics of brain regions by spectroscopic imaging

Spectroscopic imaging provides a convenient way of monitoring the lithium in different anatomical regions of the brain in a single study. Thus several pharmacokinetic profiles can be constructed in a time that is required to construct a profile from a single region of interest. Preliminary pharmacokinetic measurements in our laboratory on rat brain obtained using the SI technique have demonstrated the feasibility of this approach. Under a single 10 meq/kg IP dose of LiCl, small regions of the brain of 100 ul volume can be investigated over time. Studies have
been performed to obtain PK data on hypothalamus, cerebellum and striatal structures. As an example, the lithium PK profile for an arbitrarily chosen brain region (region 1 in Fig. 6A) is shown in Fig. 6B.

9. Brain lithium changes from drug interaction measured by $^7$Li MR

A significant fraction of patients who fail to respond to Lithium treatment alone often respond quickly when supplemented with a codrug such as an antidepressant. The resulting interaction and the codrug effect on lithium are not fully understood. A measure of the changes in the local Lithium concentration may provide clues towards the role of brain lithium in the process of mood normalization. Our preliminary studies on a rat brain model involved multiple dosing of 2 meq/kg of Li Cl and 20 mg/kg of fluoxetine over two days (5 doses). The results shown in Fig. 7A (Li alone) and Fig. 7B (Li + fluoxetine) demonstrate that lithium is increased in brain regions by a factor of about 2 when the codrug is present.

Table 3
Rat brain volumes of interest in this study (from Refs. [55–57])

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Volume estimates in microliters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>620</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>200</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>140</td>
</tr>
<tr>
<td>Hind Brain</td>
<td>140</td>
</tr>
<tr>
<td>Diencephalon</td>
<td>120</td>
</tr>
<tr>
<td>Striatum</td>
<td>120</td>
</tr>
<tr>
<td>Mid brain</td>
<td>80</td>
</tr>
<tr>
<td>Brain stem</td>
<td>60</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>40</td>
</tr>
<tr>
<td>Cingulate cortex</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 4
Human brain regions of interest for lithium imaging

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Percent of total brain volume (%)</th>
<th>Volume (ml)</th>
<th>Voxels to define the volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>~2</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Striatum</td>
<td>~6</td>
<td>90</td>
<td>28</td>
</tr>
<tr>
<td>Diencephalon</td>
<td>~4</td>
<td>56</td>
<td>18</td>
</tr>
<tr>
<td>Brain stem</td>
<td>~3</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>~12</td>
<td>168</td>
<td>52</td>
</tr>
<tr>
<td>Cingulate</td>
<td>~1.6</td>
<td>23</td>
<td>7</td>
</tr>
</tbody>
</table>

10. Prospects for Lithium studies on humans

The results from the achievable resolution for the rat brain using the 7 T system have been used as a guide to select appropriate human brain regions for $^7$Li MR studies. The study of Li distribution in broad anatomical areas such as hypothalamus, striatum, brain stem, cerebellum, diencephalons will be possible in humans under therapy. Table 3 describes the main anatomical regions which can be studied by MR. Such studies should be possible at field strengths of 3, 4 and 7 T. Studies at a reduced spatial resolution also appear possible at low field strengths such as 1.5 T. From our rat brain studies at 7 T and assuming an average SNR achievable for a given voxel volume we can predict the resolution at which human studies can be performed at field strengths varying from 1.5 to 7 T. The values shown in Table 4 are those obtained without NOE or other possible enhancements to the signal from a voxel. These results are based on the SNR value of 5 obtained from our study for 0.038 ml voxel at 7 T. The dependence of SNR on field strength was assumed to be linear. Further signal enhancements via NOE can be utilized on clinical magnets also and this should lead to improved voxel resolution and make studies at modest field strengths such as 3 T more attractive.

SNR values shown highlighted in black (Table 5) are too low to be of clinical utility. These calculations take into account (1) the $T_1$ relaxation times, (2) the coil diameter, (3)
overcome for low hydrogen nuclei and it can be expected that they will also have successfully overcome some of these problems for create more challenges. However a number of laboratories and other artifacts and unwanted power deposition will field strengths but the problems of increased susceptibility and the intensity measurements will be of clinical value.

number of voxels and hence the definition of the structures in humans, the structures can be represented by a voxel resolution are shown in Table 5. Because of the larger structures that can be studied at 3 T field strength at 3.2 ml signal to noise ratio as on 7 T systems. The various brain spatial resolution by a factor of about 4 to achieve similar in humans and rats. Studies at 3 T involve a reduction in field dependence, and (4) changes in average brain lithium concentrations closely reflect the standard in vitro results.

11. Lithium studies under constraints of specific absorption rate (SAR).

One consequence of exposure to the radio frequency fields used in MR imaging is the generation of heat in the tissue. A measure of energy or heat delivered to the tissue is the product of the power deposited and the duration of exposure [52]. The theoretical temperature rise, \( \Delta T \), for a soft tissue with specific heat of 0.83 kcal/kg\(^\circ\)C assuming no heat loss is given by: \( \Delta T = \text{SAR} \times \text{time}/3.5 \), where SAR is in units of W/Kg and time is in units of seconds. To avoid overheating any local area being examined, the product of time and local SAR should not exceed 10 W min/kg (averaged over the head) and the instantaneous SAR should not exceed 4 W/kg averaged over the head). SAR can be decreased by (a) reducing the B\(_1\) amplitude and/or the flip angle, (b) using an optimal coil configuration for the proposed studies, (c) using larger delay between pulses.

The availability of high field magnets provides increased signal to noise, improved spatial resolution, and improved spectral dispersion. However, at fields above 7 T, problems with increased susceptibility artifacts and power deposition can become more difficult. The use of a proton quadrature coil can provide up to a two-fold reduction in the power requirement [53–54]. At a field such as 4 T the use of a half-volume quadrature coil [54] has led to lower local SARs. Such a strategy can be employed, when necessary, for the lithium nucleus at 3–7 T field strengths.

12. Conclusions

Lithium in mammalian subjects can be monitored and quantified by magnetic resonance techniques in a non-invasive manner. Lithium present in different anatomical regions of the rat brain can be studied at 7 T field strength using spectroscopic imaging technology. The MR derived concentrations closely reflect the standard in vitro results.

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References
