In Vivo Imaging of the Pharmacodynamics and Pharmacokinetics of Lithium

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The therapeutic efficacy of lithium for the long-term management of bipolar disorder is well recognized, along with the risk of lithium-induced toxicity. The author describes the current findings of in vivo functional neuroimaging techniques with respect to the pharmacokinetics and pharmacodynamics of lithium and their future potential to elucidate the drug distribution and neural mechanisms that produce its therapeutic effects. Brain ^{7}Li nuclear magnetic resonance spectroscopy findings have disassociated postdose brain and blood lithium concentrations and suggest a pharmacokinetic basis for lithium response and nonresponse. The application of in vivo synaptic activity and neurochemical imaging is providing new knowledge related to the distributed neural activity associated with lithium response and is contributing to the critical human testing of neuroprotective and signal transduction models of lithium's therapeutic effects. *(J Clin Psychiatry 2000;61[suppl 9]:41–46)*

Despite 50 years of research and development toward improved agents, lithium remains unequaled in support for long-term clinical effectiveness in managing the morbidity and mortality associated with bipolar I and II disorders.[1] The many and obvious benefits of lithium to psychiatry are, however, offset by well-recognized risks related to organ toxicity. Lithium has the smallest therapeutic index of any medication routinely prescribed in psychiatry and is poorly tolerated in one third or more of treated patients. The high incidence of lithium-related adverse events[2] results in a high rate of drug noncompliance.[3] The rational use of lithium mandates the application of therapeutic drug monitoring to control for lithium-induced toxicity. It is for lithium that the promise of therapeutic drug monitoring has been best realized in psychiatry, permitting the safe use of lithium in the long-term prophylaxis of bipolar disorder. However, therapeutic monitoring of circulating lithium concentrations represents an additional deterrent to its clinical use and does not represent an ideal method of minimizing lithium-induced side effects and related drug noncompliance.

Despite the long record of successful use of lithium as a mood stabilizer, the mechanisms by which lithium produces those effects remain poorly understood. Over more than 3 decades of the clinical use of lithium in the United States, the mechanisms thought to underlie its therapeutic effects have been many in number, although they typically fail to withstand further scrutiny. It is increasingly clear that lithium's therapeutic effects represent a composite of multiple effects on cellular function. Currently, the best evidence supports lithium's effects on signal transduction pathways and programmed gene expression as being best related to its mood-stabilizing effects.[4,5] Moreover, a clear understanding of the mechanisms of lithium's therapeutic effects seemingly holds an important key to a larger understanding of the mysteries of the pathophysiology of mood disorders. At the center of this search will be the role of new technologies to probe the effects of lithium on human brain function. In vivo functional neuroimaging techniques have provided an increasingly fine-grained analysis of the relationship between the brain and behavior, and in doing so, transformed the field of psychiatry research. This work describes the present state and future potential of functional brain imaging approaches to an improved knowledge of the pharmacokinetics and pharmacodynamics of lithium in the treatment of mood disorders.

IMAGING LITHIUM PHARMACOKINETICS IN VIVO

The clinical use of lithium in the treatment of bipolar disorder has been inextricably tied to the practice of therapeutic drug monitoring. While psychiatrists differ in the frequency of venipuncture sampling to support quantitative lithium determinations, the great majority, if not all, psychiatrists base the safe use of lithium on obtaining blood lithium concentration values as reference points. Serum lithium concentrations of 0.5–1.2 mM are generally adhered to as the window within which the highest probabil-

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ity of therapeutic responses uncomplicated by serious adverse events are obtained. Organ toxicity is often encountered when the serum concentration of lithium exceeds 1.5 mM.[6] Life-threatening intoxication is often associated with serum lithium concentrations exceeding 3.5 mM.

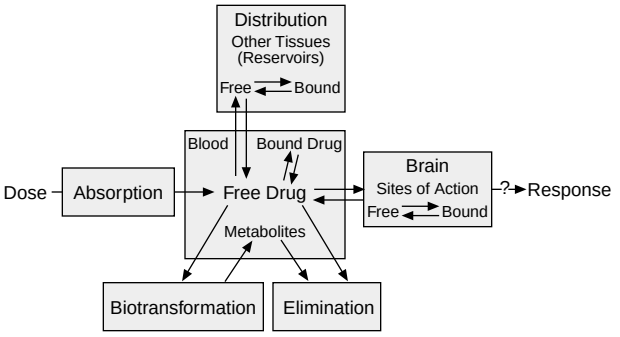
It is, however, important to note that exceptions to these concentration-effect relationships are frequently seen. Some patients obtain therapeutic benefits of lithium at serum lithium concentrations less than 0.5 mM or require serum concentrations exceeding 1.2 mM. Moreover, adverse events can occur at serum lithium concentrations in the nominal therapeutic range. The attainment of serum lithium concentrations within this therapeutic range also does not ensure treatment response in 20% to 30% of patients for whom lithium pharmacotherapy is indicated. Perhaps the most plausible initial explanation for these cases would be that individual differences in lithium pharmacodynamics distinguish these different groups of patients. However, an increasingly plausible explanation may relate to individual differences in the pharmacokinetics of lithium as regards its distribution to sites of action in the central nervous system (CNS). A critical assumption to the general application of lithium therapeutic drug monitoring is that the circulating concentration of lithium reliably reflects the concentration of lithium at extracellular sites of action in the CNS. This assumption has been unchallenged since this latter compartment had been impenetrable until the recent addition of ^{7}Li nuclear magnetic resonance (NMR) spectroscopy (MRS).

Figure 1 illustrates the pharmacokinetic and pharmacodynamic events that define the dose-response relationship for psychoactive medications. Drug absorption, distribution, metabolism, and elimination define their pharmacokinetics. The specific pharmacodynamic events that transduce the interactions of nonbound drug in the brain extracellular space with its molecular sites of action (e.g., neurotransmitter transporters or receptors, genes) to therapeutic response are increasingly understood. These interactions and effects constitute the drug pharmacodynamics. The promise of therapeutic drug monitoring to optimize and individualize the efficacy and safety of medications is largely based on the ability of an accurate determination of circulating drug concentration to control for individual and time-dependent differences in pharmacokinetics, and thus abbreviate the dose-effect relationship to that of a less varying concentration-effect relationship (see Figure 1).

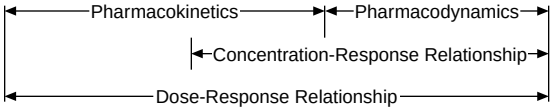
The practice of therapeutic drug monitoring has enabled a widespread clinical use of lithium, a drug that has the lowest therapeutic index of any drug routinely prescribed in psychiatric medicine. This is in large part due to the unique pharmacokinetic properties of lithium (see Figure 1C). Lithium exhibits negligible binding to plasma proteins, does not undergo biotransformation, and is eliminated by a virtually exclusive renal route.[7] These properties simplify greatly the role of individual pharmacokinetic

Figure 1. Pharmacokinetic and Pharmacodynamic Events That Define the Dose-Response Relationship for Psychoactive Medications

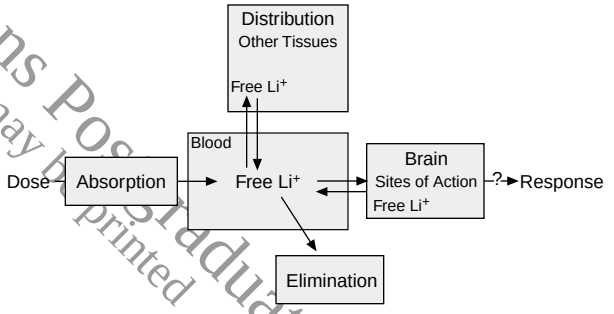
A. Relationship between drug pharmacokinetics and pharmacodynamics in defining the dose-response relationship



B. Theoretical basis for the use of therapeutic drug monitoring in optimizing and individualizing pharmacotherapy



C. Dose-response model reflecting the unique pharmacokinetic properties of lithium



differences in defining lithium dose- and concentration-effect relationships in its clinical use. However, at steady-state lithium dosing, different tissues reflect markedly different lithium concentrations. Lithium concentrations in the systemic circulation are approximately twice that found in red blood cells, muscle, and cerebrospinal fluid and similar to values observed in heart and lung.[6] The activity of sodium-lithium countertransport mechanisms variably expressed in different tissues and other mechanisms may explain, at least in part, this differential lithium distribution at steady state.

Brain imaging techniques such as MRS are providing new insights into the distribution and other aspects of the human pharmacokinetics of lithium that may contribute to an improved understanding of the basis of lithium response and nonresponse. Lithium has 2 naturally occurring

isotopes: ^{6}Li and ^{7}Li. The proton nuclei of the hydrogen atom (^{1}H) possess a small magnetic moment that forms the basis of the molecular signal used in modern anatomical magnetic resonance imaging (aMRI). The ^{7}Li isotope similarly possesses a small magnetic moment. Therefore, in a like manner, the localization of lithium can be determined by ^{7}Li MRS using techniques similar to ^{1}H MRI. In MRI, the angular momentum or "spin" of such anatomic nuclei in a main magnetic field is encoded as to spatial position with distinct NMR frequencies by the application of a magnetic field across the sample.[8] The resolution of the resulting MR signal in a single dimension is a product of the magnetogyric ratio (proportional to the magnetic moment of the isotope of interest), the strength of the applied magnetic field gradient, and the image acquisition time. For ^{7}Li, the sensitivity for an equal number of atoms is 27% that of ^{1}H. The initial challenge to ^{7}Li MRS was that the tissue concentration of ^{7}Li following therapeutic doses is small relative to the 80–100 M concentration for water hydrogen. The low relative concentrations of ^{7}Li result in less than ideal signal-to-noise (S/N) ratios and the need for longer image acquisition times. Early ^{7}Li MRS studies therefore were based on a poor ability to spatially resolve ^{7}Li signals and characterized by relatively large volume elements (voxels) to interrogate the in vivo organ distribution of lithium following dosing. The sensitivity and specificity of ^{7}Li signals have, however, been improved by the use of improved coils, higher main field strengths, use of a standardized brain volume, and more accurate estimates of T_1 and T_2 relaxations for ^{7}Li.

^{7}Li MRS has furnished new knowledge regarding the human brain pharmacokinetics of lithium and the relationship of brain lithium concentrations to daily dose and clinical state.[7] Brain lithium concentrations following oral dosing exhibit a delayed uptake and elimination compared with the blood compartment.[9] In vivo ^{7}Li MRS also indicates a variable relationship between brain and blood lithium concentration and daily dose. Brain/serum lithium concentration ratios of 0.1–1.0 have been observed following prolonged lithium administration.[10,11] Brain and serum lithium concentrations are only moderately correlated, and the ratios between the 2 fluctuate by 2- to 3-fold over a 48-hour period.[12] Moreover, brain lithium concentrations were only weakly correlated with serum lithium concentrations in the range of 0.6–1.7 mM.[13] The disconnect between brain and serum lithium concentrations following oral lithium dosing also is demonstrated by substantial interindividual differences in brain lithium concentration at similar serum lithium concentrations.[14] Brain lithium concentrations were significantly correlated with daily lithium dose following long-term (> 6 mo) but not short-term (1–2 mo) administration.[15] At least one study[10] reported a better correlation with clinical improvement in the treatment of mania for brain versus serum lithium concentrations. As yet, ^{7}Li MRS–defined brain lithium concentrations have not distinguished between lithium responders and nonresponders.[11]

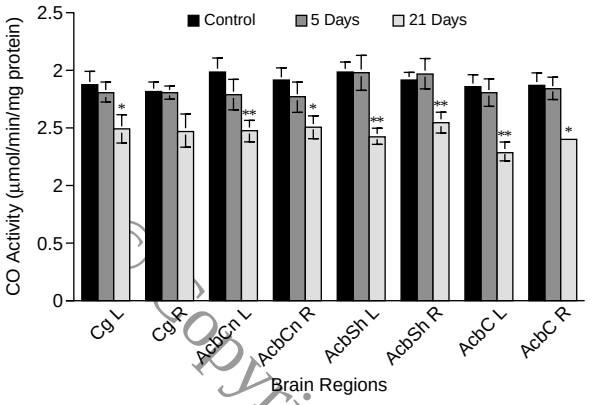
Brain ^{7}Li MRS is forcing new thinking regarding the relationship between the blood and brain compartments for lithium and in doing so questions a fundamental basis for therapeutic drug monitoring for lithium. While ^{7}Li MRS is obviously not feasible as a substitute for venipuncture in routine therapeutic drug monitoring, it does provide insights into the basis for therapeutic failure and adverse events observed in individuals with serum lithium concentrations falling within the nominal therapeutic range. The question as to whether an abnormal brain lithium concentration following oral lithium dosing is associated, in some patients, with treatment nonresponse remains to be determined. The future ability to interrogate the brain regional distribution of lithium following oral dosing using smaller voxels may ultimately define the concentration-effect relationship for the use of lithium in the treatment of bipolar disorder and ultimately resolve the pharmacokinetic role in lithium nonresponse.

IMAGING THE PHARMACODYNAMICS OF LITHIUM

How does this small monovalent cation produce its remarkable mood-stabilizing effects? This question has intrigued many a neuroscientist and spawned many a mechanistic model. The value of such models has been closely tied to the ability of the proposed mechanism to model the delayed onset of therapeutic effects of lithium with repeated dosing. It is not the intent of this discussion to review the history of development and testing of such models, but rather to illustrate the current and future contributions of functional brain imaging to the testing and reformulation of such models. In this regard, this discussion will emphasize the specific use of such techniques in mapping lithium-related changes in synaptic activity and in vivo neurochemistry.

Positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI) have provided powerful insights as to the distributed neural processing that defines behavior. While such techniques have recently been used to initiate the definition of a functional neuroanatomy of bipolar disorder, their use in defining the neural correlates of the therapeutic effects of lithium has not to our knowledge been attempted. The results of a recent in vitro molecular imaging study from an animal model[16] may furnish anatomical targets to be used as regions of interest for such an analysis. This study sought to inform the biological basis of lithium's mood-stabilizing effect by mapping the anatomy of neural systems functionally changed by chronic lithium administration in a rodent model. Mapping involved the in vitro histochemistry of the activity of cytochrome oxidase (CO), the terminal enzyme of the electron transport chain,

Figure 2. Rodent Model of Neural System Changes Caused by Chronic Lithium Administration[a]



[a]From Lambert et al.,[16] with permission. Histogram showing mean cytochrome oxidase (CO) activity (± SEM) in cingulate cortex (Cg) and subterritories of the nucleus accumbens (AcbCn, AcbSh, AcbC) in rats fed standard rat chow (control) or rat chow containing 0.1% (by weight) lithium carbonate for 5 or 21 days.
*$p < .05$.
**$p < .01$.

which is regulated by and closely correlated with neuronal functional activity.[17] Observed changes in brain CO activity were dependent on the duration of oral lithium administration and were brain-region selective.[16] Compared with nontreatment (control), oral lithium administration for 5 consecutive days had no effect on CO activity within any brain region examined. However, oral lithium administration for 21 consecutive days significantly altered CO activity in the cingulate cortex and the core, shell, and cone subterritories of the nucleus accumbens where a significant decrease was observed (Figure 2). Serum lithium concentrations were similar following 5 or 21 days of lithium treatment. Fulfilling the criterion of a delayed onset of effect, these results suggest a treatment response–related effect of lithium on neural activity in ventral striatal and paralimbic brain regions.

In a secondary analysis, the study of interregional correlations of effects of lithium on CO activity suggested neural pathway–dependent effects of prolonged versus short-term lithium administration.[16] Compared with 5-day lithium treatment, 21 days of lithium administration resulted in new significant correlations between the cingulate cortex and both the frontal cortex and nucleus accumbens; correlation between these latter 2 regions and the thalamus was weakened. The lithium-induced alterations in interregional correlation coefficients were primarily localized to the left hemisphere. These results suggest that lithium's antimanic effects may relate to altered neural processing in paralimbic-frontal-striatal pathways, with the left hemisphere being preferentially affected. The effects on frontal cortical function are consistent with other results from animal studies demonstrating chronic lithium treatment–induced decreases in immediate early gene expression in the frontal cortex[18] and an increased density of frontal cortical serotonin transporters.[19] Perhaps most importantly, these same brain regions implicated by this molecular imaging study in a rodent model as being involved in the effects of prolonged lithium treatment have been implicated in mood disorders and the therapeutic effects of lithium in imaging studies in humans. Lithium withdrawal in a sample of bipolar patients was associated with the development of manic symptoms and a significant increase of regional cerebral blood flow in the anterior cingulate cortex.[20] These data suggest that during mania synaptic activity is increased within selective cortical areas, particularly the anterior cingulate, and that suppression of this overactivity may be important to the antimanic effects of lithium. The significance of these studies is that they provide defined regions of interest for the future use of in vivo synaptic activity imaging techniques such as PET and fMRI to a study of the interaction of lithium with mania.

The foregoing discussion represents efforts directed toward understanding the "final common pathway" of lithium's antimanic effects and would presumably reflect the integration of lithium's many described effects on transsynaptic signaling pathways and gene expression.[5] Functional brain imaging techniques also have clear and promising applications in testing and reformulating hypothetical mechanisms of lithium's antimanic effects exerted at cellular and subcellular levels. As previously discussed, such mechanistic models must incorporate the fact that therapeutic effects of lithium necessitate its prolonged administration and are associated with a clear delay in onset. This delayed onset has suggested to further implicate psychotropic drug-induced alterations at the genomic level.[21] The search for lithium-induced changes in gene expression that may be related to its mood-stabilizing effects has resulted in novel and potentially important mechanisms suggesting a neuroprotective effect of lithium.[5] A series of investigations following on the results of the effect of chronic lithium administration on differential gene expression in rats led to the demonstration of lithium-induced increases in the levels of the neuroprotective protein B-cell lymphoma/leukemia-2 gene product bcl-2 in the frontal cortex, hippocampus, and striatum.[22] A recent MRS study sought to determine whether lithium may exert neurotrophic/neuroprotective effects in the human brain in vivo. Model testing involved the use of MRS as a functional neurochemistry imaging tool to assess the effects of lithium on brain *N*-acetyl-aspartate (NAA). NAA is a putative marker of neuronal viability and function. Compared with a baseline measure, 4 weeks of lithium administration resulted in a significant increase in total brain NAA concentration in 21 subjects (12 medication-free bipolar disorder patients and 9 healthy volunteers).[23] Lithium-induced increases in NAA concentration were observed in the frontal, temporal, parietal, and occipital

lobes. These in vivo ^{1}H MRS studies are consistent with the contention that chronic lithium administration enhances neuronal viability/function in the human brain and suggest that neurotrophic/neuroprotective events may underlie some of lithium's efficacy in the management of bipolar disorder.

In vivo ^{1}H MRS has also played a role in the human testing of signal transduction pathway models of lithium's efficacy as a mood stabilizer. The role of the phosphoinositide (PI) transduction cascade as a potential target of lithium's actions represents arguably the most widely adhered to of such models. At therapeutically relevant concentrations, lithium represents, in vitro, an inhibitor of inositol monophosphatase and other enzymes involved in recycling inositol phosphates and supporting neurotransmitter receptor–mediated PI turnover. By these actions, the therapeutic effects of lithium have been proposed to be the result of inositol depletion. In a recent test of the inositol depletion hypothesis, Moore and colleagues[24] examined longitudinal measures of frontal cortical *myo*-inositol concentrations using quantitative proton MRS. Significant decreases in right frontal cortical *myo*-inositol were observed following both acute (5–7 days) and chronic (3–4 weeks) lithium administration to 12 adult depressed patients. The fact that frontal cortical *myo*-inositol decreases were observed following acute lithium administration at a time when the patient's clinical status was unchanged suggests that lithium effects on brain *myo*-inositol are not directly associated with therapeutic response. Some support for the inositol depletion hypothesis is, however, derived from a separate in vivo ^{1}H MRS study.[25] Compared with placebo, lithium administration to healthy volunteers resulted in an increase in frontal cortical inositol phosphate accumulation when MRS measures were coupled with an amphetamine-stimulated PI cycle. The fact that this effect of lithium was observed following 8 days of lithium administration, however, continues to question the role of this effect in lithium's therapeutic use. Finally, a recent in vivo ^{1}H MRS study[26] of basal ganglia choline-containing compounds failed to demonstrate a difference between bipolar disorder patients with and without lithium treatment. These studies highlight the present and future potential of the use of in vivo quantitative ^{1}H MRS to test mechanistic models of lithium's therapeutic effects.

SUMMARY

Despite recent challenges, lithium remains unsurpassed in therapeutic efficacy in the management of bipolar disorder. In vivo brain imaging techniques offer new access to the previously impenetrable brain compartment for lithium distribution. These methods are providing new insights into the role of pharmacokinetics in defining lithium response and nonresponse. Imaging techniques stressing synaptic activity mapping and quantitative in vivo determinations of functional neurochemistry are similarly providing new insights into the neural processing and cellular and subcellular actions of lithium that underlie its therapeutic efficacy. These latter approaches will be critical to the human testing of mechanistic models derived from preclinical science.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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