
INTRODUCTION

Lithium: A Molecular Transducer of Mood-Stabilization in the Treatment of Bipolar Disorder

Lithium is an element discovered over 175 years ago (1817), and over the ensuing period of time, it has been utilized in various formulations as a remedy for a multitude of maladies afflicting the human body (Johnson 1984); however, it was not until its serendipitous rediscovery and the seminal work of Australian physician/scientist, John Cade, 45 years ago, and subsequent clinical studies by Mogens Schou in the early 1950s, that lithium was seen by modern psychiatry as an effective antimanic treatment and a prophylactic therapy for manic-depressive illness (bipolar affective disorder, BD) (Cade 1949; Schou 1979). The discovery of lithium's efficacy as a mood-stabilizing agent revolutionized the treatment of patients with BD—indeed, it is likely that the remarkable efficacy of lithium has, in fact, served to spark a revolution that has, over time, reshaped not only medical and scientific, but also popular concepts of severe mental illnesses. After nearly three decades of use in North America, lithium continues to be the mainstay of treatment for this disorder, both for the acute manic phase and as prophylaxis for recurrent manic and depressive episodes (Goodwin and Jamison 1990; Lenox and Manji 1995). Adequate lithium treatment, particularly in the context of a lithium clinic, is also reported to reduce the excessive mortality observed in the illness (Baldessarini and Tondo 1997; Muller-Oerlinghausen et al. 1992; Vestergaard and Aagaard 1991), and it has been estimated that in most industrialized countries, 0.1% of the population is undergoing lithium treatment (Schou 1991). The effect on the broader community is highlighted by one estimation that the use of lithium saved the United States \$4 billion in the period 1969–1979 by reducing associated medical costs and restoring productivity (Reifman and Wyatt 1980). However, despite its role as one of psychiatry's most important

treatments (Goodwin and Jamison 1990; Schou 1991), the biochemical basis for lithium's antimanic and mood-stabilizing actions remains to be fully elucidated (Lenox and Manji 1995; Manji et al. 1995). Elucidation of the mechanism(s) by which lithium stabilizes an underlying dysregulation of limbic and limbic-associated function also offers the potential to delineate the underlying etiology/pathophysiology of BD (Lenox et al. 1987; Manji et al. 1995). The recognition of the significant morbidity and mortality of the severe mood disorders, as well as the growing appreciation that a significant percentage of patients respond poorly to existing treatments has made the task of discovering new therapeutic agents that work quickly, potently, specifically, and with few side effects increasingly more important. Indeed, in a recent article discussing the major impact this monovalent cation has had on psychiatry, Schou (1997) expressed his disappointment that we have yet to elucidate fully the mechanisms by which lithium exerts its therapeutic effects. However, there has been tremendous recent progress not only in the identification of signal transduction pathways as biochemical targets of lithium's actions, but also in characterizing dimensional features of BD that may confer differential treatment responsiveness. This issue of *Neuropsychopharmacology*, for which Husseini K. Manji, M.D., and Robert H. Lenox, M.D. serve as guest editors, pays tribute to the seminal the work of John Cade, which has had a truly remarkable impact on the lives of millions throughout the world. The following peer-reviewed papers represent the thoughtful insights of some of the leading preclinical and clinical researchers brought together at the CINP meeting in Melbourne, Australia to provide a series of presentations focusing upon the current conceptualization about the neurobiology of BD

and the clinical and biochemical effects of mood-stabilizing agents.

The clinical chapters are state-of-the-art discussions of key issues in the field. The first two papers provide apparently differing perspectives for a very fundamental research and treatment question—the specificity of lithium's effects in BD.

Soares and Gershon present a compelling argument that lithium shows a specificity for bipolar disorder—an idea that was, in fact, proposed in Cade's original 1949 work. They review the many controlled studies that have been carried out, examining lithium for treatment of bipolar disorder and other psychiatric conditions. The authors conclude that the data analyzed give strong support for lithium being most effective for bipolar disorder, with minimal or no therapeutic effects in other neuropsychiatric disorders. Such findings clearly have major implications for the field, because they may lead to meaningful contributions to understanding the pathophysiology of bipolar disorder and help to develop newer treatments for this condition.

In his paper, *Grof* suggests that lithium treatment, initially considered specific for bipolar disorder, has later been shown to provide additional benefits in affective and other disorders. He further states that a variety of benefits should be taken into account when interpreting recently reported lower efficacy during lithium prophylaxis, as well as early relapses and loss of efficacy after lithium discontinuation. He provides a compelling argument that other factors, such as the accumulation of atypical, treatment-resistant patients in academic centers and in particular the broadening of diagnoses of affective disorders must be considered and that these factors have complicated the interpretation of the recent reports. There seems to be little question, however, that lithium continues to work well for patients with typical bipolar disorders for whom it was originally proved effective. The author has addressed an important issue relating to evaluating the specificity of any treatment modality when clinical practice extends its use to other disorders for which there is variable therapeutic efficacy.

Dunner addresses an increasingly appreciated clinical question in the long-term study and treatment of BD—the potential role of rapid cycling as a modifier of the course of the illness. Originally defined as four or more affective episodes per year by Dunner and Fieve in 1974, rapid-cycling BD has now become recognized as having major implications for the choice of treatment. As such, there is a growing consensus that rapid cycling be included as a course modifier to bipolar disorders in the *DSM-IV*. Dunner reviews the process for inclusion of rapid cycling as a course modifier to bipolar disorders in *DSM-IV*; this process has involved defining bipolar II disorder, delineating the duration of manic episode for bipolar I disorder, and clarification of the diagnosis of cyclothymic disorder and mixed ma-

nia. These classifications will likely lead not only to improved research studies of more homogeneous populations of BD patients, but may also serve to improve overall individualized treatment delivery, in particular, further defining the use of lithium and anticonvulsants in the treatment of BD.

The possibility that antiepileptic drugs might have efficacy in bipolar disorder has encouraged early clinical studies with several newer antiepileptic drugs—in his paper, *Bowden* presents data supporting the effectiveness of valproate and lamotrigine. He reaffirms the data that the spectrum of efficacy of valproate may be somewhat broader than that of lithium, and further presents data from a study suggesting that pretreatment plasma GABA is positively correlated with magnitude of improvement in manic symptomatology with valproate. Although the source and significance of plasma GABA remains to be fully elucidated, these findings deserve to be replicated in our efforts to search for a biological marker predictive of treatment response. In addition, *Bowden* comprehensively reviews the emergence of valproate as a powerful lithium alternative, and/or adjunct, and further reviews the preliminary, but intriguing indications that lamotrigine may offer promise as an even more effective treatment for the *depressive* phases of bipolar illness.

Johnson, in his erudite paper, discusses an issue that has sometimes led to rejection of lithium on safety grounds—lithium's potential adverse effects on renal function. He provides a fascinating historical overview regarding lithium's development in the treatment of mania, outlining the way in which the report of the effectiveness of lithium in the treatment of mania by John Cade (1949) was followed by a number of studies confirming his observations and developing guidelines for safe and effective use. He discusses the "safety alarms" that were triggered by reports of kidney damage in the late 1970s. Although at one time it was widely feared that lithium treatment might lead to a decrease in the glomerular filtration rate, systematically collected data indicate that even long-term treatment does not induce renal insufficiency. In fact, it now seems clear that progressive impairment of glomerular and tubular function in patients during lithium maintenance is the exception rather than the rule and that it is related more to lithium intoxication, maintenance plasma lithium levels, concurrent medications, somatic illness, and age than the duration of lithium treatment. *Johnson* concludes his paper by outlining practical guidelines for lithium use and monitoring of renal function.

Post and associates present an integrated preclinical/clinical overview for the neurobiology of BD and its treatment under different illness stages by combination treatments, in particular with anticonvulsants. This research group has been instrumental in outlining molecular mechanisms involved in the evolution of amygdala

kindling and the episodic loss of response to pharmacological treatments during tolerance development. They have postulated that similar principles could account for illness progression, cyclicity, and drug tolerance in affective disorders. Post and associates describe the experimental paradigms under which, amygdala-kindled animals that were initially drug responsive can develop highly individualized patterns of seizure breakthroughs progressing toward complete loss of drug efficacy. Their clinical studies intertwine very nicely with the proposed preclinical model and suggest that BD represents a syndrome that, for many patients, is not readily treated by single agents. The authors provide compelling data that, in many instances, anticonvulsant drugs are effective alone or in combination with lithium in those patients less responsive to lithium monotherapy, including those with greater numbers of prior episodes, rapid cycling, dysphoric mania, co-morbid substance abuse, or other associated medical problems, as well as patients without a family history of bipolar illness in first-degree relatives. Thus, anticonvulsants are widely used and are now recognized as major therapeutic tools for lithium refractory BD. Preliminary controlled clinical trials suggest that certain calcium channel blockers may have antimanic or mood-stabilizing effects in a subgroup of patients. They conclude by suggesting that exploration of the optimal use of lithium and the mood-stabilizing anticonvulsants alone and in combination, as well as with other adjunctive treatments, is now required so that more definitive treatment recommendations for different types and stages of BD can be more objectively based.

Belmaker and associates provide a description of an integrated series of studies examining the "inositol depletion hypothesis" for the mechanism of action of lithium. It is now well established that lithium, at therapeutically relevant concentrations, is a potent inhibitor of inositol monophosphatase (Ki, 0.8 mM); this has been demonstrated to result in an accumulation of inositol-1-monophosphate (Ins(1)P) as well as a reduction in free inositol (Allison and Stewart 1971; Hallcher and Sherman 1980). Because the ability of a cell to maintain sufficient supplies of *myo*-inositol is crucial to the resynthesis of the phosphoinositides and the maintenance and efficiency of signaling, and because the mode of enzyme inhibition is *uncompetitive*, lithium's effects have been postulated to be most pronounced in systems undergoing the highest rate of PIP₂ hydrolysis (Berridge et al. 1982, 1989). It has thus been suggested that a physiological consequence of lithium's action is derived through a depletion of free inositol (Berridge et al. 1982, 1989). Thus, the inositol depletion hypothesis has garnered much support as a mechanism to explain how this seemingly simple monovalent cation could exert such a profound impact on arguably one of the most complex of all mental illnesses. However, as *Belmaker*

and associates review, the inositol depletion hypothesis of lithium action has been increasingly criticized because depletion of inositol after chronic lithium treatment has not been reproducible, because effects of inositol to reverse lithium-induced behaviors occurred also with epi-inositol, an unnatural isomer, and because inositol is ubiquitous in brain and difficult to relate to the pathogenesis of affective disorder. They review their research group's studies showing that lithium depletion of brain inositol occurs chronically in the hypothalamus, a region that has not been previously examined. They further demonstrate that the behavioral effects of four different inositol isomers (including epi-inositol) correlate well with their biochemical effects. Finally, they show that inositol in postmortem human brain is reduced by 25% in frontal cortex of patients with BD and patients committing suicide as compared with controls. Because recent human studies utilizing *in vivo* magnetic resonance spectroscopy (MRS) have demonstrated that lithium *does* indeed lower *myo*-inositol levels in frontal cortex (Moore et al. 1997), and because coadministration of *myo*-inositol does attenuate some of lithium's effects on signal transduction pathways (Lenox et al. 1996; Manji et al. 1996a), it is clear that lithium (in a therapeutically relevant paradigm) does affect *myo*-inositol. However, because *myo*-inositol in postmortem brain is *reduced* and not *increased* in bipolar patients, and because the authors have observed that some effects of chronic *myo*-inositol seem similar to that of chronic lithium (Manji et al. 1996a), the relationship between *myo*-inositol, lithium, and affective disorder seems to be complex.

Mori and associates have studied the effects of lithium on the other major transmembrane signaling system, the cAMP second messenger system. Over the years, a large body of data (utilizing membrane, slice, and synaptosomal preparations from rat brain *in vitro* and *ex vivo*, peripheral cells from humans, and postmortem human brain tissue) has confirmed that lithium has significant effects on the cAMP second messenger generating system in rodents and in humans (reviewed in Mork et al. 1992; Lenox and Manji 1998; Manji et al. 1995). *Mori* and associates have investigated the effects of lithium treatment on cAMP-dependent protein kinase in discrete brain areas of rat by using photoaffinity labeling as well as western blotting. They demonstrate that chronic (5 week) lithium administration resulted in a significant increase of the cAMP binding to the 52 kDa cAMP-receptor in the soluble, but not in the particulate, fractions of both hippocampus and frontal cortex. Accompanying these novel results, they find that chronic lithium treatment significantly increased the immunoreactivity against the regulatory and the catalytic subunits of the cAMP-dependent protein kinase in the soluble fraction of both brain areas. Intriguingly, no significant effects were observed in the particulate fractions. In contrast, *Mori* and associates have found that

short-term (6 days) lithium treatment induced a significant increase in the immunolabeling of the catalytic subunits in the soluble fraction of both areas; whereas, the regulatory subunits and the actin were unchanged. Although they did not observe any differences in actin levels, it is noteworthy that a target of lithium—MARCKS—cross links filamentous actin and has been implicated in cellular processes including cytoskeletal restructuring, transmembrane signaling, and neurotransmitter release (Blackshear, 1993); actin may, thus, represent an indirect target for lithium's actions. The results of their study give additional evidence that components of the cAMP signaling system also may play a role in lithium's biochemical actions.

The papers in this issue of *Neuropsychopharmacology* clearly show that John Cade's seminal work demonstrating lithium's efficacy not only launched the psychopharmacological revolution, but its effects on multiple aspects of BD presented an irresistible scientific challenge—one that clearly has been accepted by the scientific community. The large second revolution in psychopharmacology of the 1980s and 1990s, with serotonin-specific reuptake blockers and atypical antipsychotics, seemed to leave BD on the sidelines. That period is not clearly over. Carbamazepine, valproate, and lamotrigine, along with other new anticonvulsants (and potentially antibipolar drugs) still in the pipeline, as well as completely novel agents such as protein kinase C inhibitors (Bebchuk et al. 1997), all have the potential to revolutionize clinical practice, while at the same time providing exciting new hypotheses relating to the pathophysiology of BD. We still have much to learn about lithium's actions, but the rate of progress in recent years has been exciting indeed. Lithium is a monovalent cation with complex physiological and pharmacological effects within the brain. By virtue of the ionic properties it shares with other important monovalent and divalent cations such as sodium, magnesium, and calcium, its transport into cells provides ready access to a host of intracellular enzymatic events affecting short- and long-term cell processes. It may be that, in part, the therapeutic efficacy of lithium in the treatment of both poles of manic-depressive disorder may rely on the "dirty" characteristics of its multiple sites of pharmacological interaction.

Strategic models to delineate further the mechanism(s) of action of lithium relevant to its therapeutic effects must account for a number of critical variables in experimental design. Lithium has a relatively low therapeutic index, requiring careful attention to the tissue concentrations at which effects of the drug are being observed in light of the known toxicity of lithium within the CNS. Although such a low therapeutic index may suggest a continuum between some of the biological processes underlying therapeutic efficacy and toxicity, it may also account in part for the variability of effects

of lithium observed in animal and *in vitro* studies. The therapeutic action of lithium is delayed, requiring more long-term administration to establish efficacy for both its treatment of acute mania and its prophylaxis of the recurrent affective episodes associated with BD. Although its therapeutic effects are not reversed immediately with abrupt discontinuation, there is accumulating evidence that abrupt withdrawal of lithium may sensitize the patients's system to an episode of mania (Goodwin and Jamison 1990; Suppes et al. 1991; Faedda et al. 1993).

The ability of lithium to stabilize an underlying dysregulation of limbic and limbic-associated function is critical to our understanding of its mechanism of action. The biological processes in the brain responsible for the episodic clinical manifestation of mania and depression may be caused by an inability to mount the appropriate compensatory responses necessary to maintain homeostatic regulation; thereby, resulting in sudden oscillations beyond immediate adaptive control (Depue et al. 1987; Goodwin and Jamison 1990; Mandell et al. 1984). The resultant clinical picture is reflected in disruption of behavior, circadian rhythms, neurophysiology of sleep, and neuroendocrine and biochemical regulation within the brain. Regulation of signal transduction within critical regions of the brain remains an attractive target for psychopharmacological interventions. The behavioral and physiological manifestations of the illness are complex and are mediated by a network of interconnected neurotransmitter pathways.

It is our strong conviction that it is at the cellular and molecular level that some of the most exciting advances in our understanding of the long-term therapeutic action of lithium will take place in the coming years. In recent years, it has become increasingly appreciated that any relevant biochemical models proposed for the effects of many psychotropic drugs (including mood-stabilizers) must attempt to account for their special temporal clinical profile. In particular, the therapeutic effects of lithium require a lag period for onset of action and are generally not immediately reversed upon discontinuation. Such a temporal pattern of effects requiring prolonged administration of the drug suggest alterations at the genomic level (Manji et al. 1995; Hyman and Nestler, 1996). Current studies of the long-term lithium-induced changes in the phosphoinositide and PKC signaling pathways (including *myo*-inositol, diacylglycerol, and PKC isozyme regulation, post-translational modification of important phosphoproteins implicated in signaling and neuroplastic changes, as well as PKC-mediated gene expression) are most promising avenues for investigation. This is particularly significant in light of converging data from studies of the structurally dissimilar mood-stabilizing agents lithium and valproate (VPA), relating their therapeutic efficacy to the regulation of PKC isozymes, the transcriptional expression of the PKC substrate, MARCKS, and long-term modulation of

membrane-related events involving cytoskeletal restructuring, such as ion transport, neurotransmitter release, and the receptor-response complex (Manji et al. 1996b; Watson and Lenox 1996). In addition, it is noteworthy that lithium, at clinically relevant concentrations, has recently been demonstrated to inhibit the activity of glycogen synthase kinase-3 (GSK-3) (Hedgepeth et al. 1997; Klein and Melton 1996; Stambolic et al. 1996). Glycogen synthase kinase-3 (GSK-3) is known to phosphorylate c-jun at three sites adjacent to the DNA binding domain, thereby reducing TRE binding (Lin et al. 1993; Stambolic et al. 1996). Interestingly, VPA, at therapeutically relevant concentrations, has also recently been demonstrated to inhibit the activity of GSK α and GSK β (Chen et al. 1997).

In this context, it is also evident that lithium, at therapeutically relevant concentrations, can stimulate gene expression through the activator protein (AP-1) transcription factor pathway in the CNS and in human neuronal cells (Chen et al. 1998; Ozaki and Chuang 1997; Yuan et al. 1998). The precise mechanisms by which lithium brings about these changes remains to be fully elucidated. The AP-1 transcription factors are the downstream targets of mitogen activated protein kinases (MAPK) pathways (Karin 1995; Whitmarsh and Davis 1996), and several lines of evidence have indicated protein kinase C (PKC) activates these pathways (Whitmarsh and Davis). In view of the evidence demonstrating significant effects of lithium on the PKC signaling pathway (reviewed in Jope and Williams 1994; Manji and Lenox 1994; Manji et al. 1995), it is likely that lithium regulates AP-1 DNA binding activity, at least in part, via the PKC-MAPK pathways and cross talk via inhibition of GSK-3. Among the many genes in the brain known to be driven by AP-1 containing promoters are those for key enzymes involved in neurotransmitter synthesis, neuropeptides, neurotrophins, and transcription factors (Hunges and Dragunow 1995), which can provide a biological basis for the long-term therapeutic action of lithium in stabilizing the course of BD (Chen et al. 1998). In addition, it is likely that forthcoming research along these lines will lead to further insight into the pathophysiology of BD.

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