Lithium- an update on the mechanisms of action

Part one: pharmacology and signal transduction

Jose Segal
Division of Psychiatry,Faculty of Health Scences, University of the Witwatersrand, Johannesburg, South Africa

Abstract
Lithium has been used clinically for about 50 years. Only in the last several years however has there been a rapid growth in our understanding of its biochemical effects. It is now clear that lithium has a complicated multitude of diverse effects in the human nervous system. This new data is helping us understand the neurobiology of bipolar disorder. The focus of this review will be to distil this new knowledge into a form that will be accesible to the clinician. It will be presented in two parts. Part one will deal primarily with pharmacology and neuronal signal transduction. Part two will focus principally on neural effects and neuroanatomical substrates. This review is designed to help the embattled clinician at the coalface stay abreast of the recent advances in this complicated field. An exhaustive in-depth analysis of biochemical action is not the intention of this work.

Keywords: *Lithium, Pharmacology, Signal transduction, Bipolar disorder*

Lithium is effective for the management of bipolar disorder in all its various forms i.e. acute, prophylaxis and maintenance phases.[1-9] After almost 5 decades of experience, lithium's clinical benefits and shortcomings should be established beyond doubt. Lithium has been described as "well established",[10] "one of the most rewarding therapeutic strategies"[11] and that it has "sufficient evidence to justify its use".[12] However, it has also been stated that there is "little evidence that lithium is effective".[13]

In spite of contradictory statements regarding usage our understanding of the mechanisms of action of lithium have increased. Very detailed and complicated review articles have been published.[14-19] Part one of this review will focus on our new understanding of the pharmacological principles behind lithium's therapeutic effects. Thereafter the review will examine the impact on signal transduction, including the multitude of ionic and neurotransmitter effects as well as the impact on G proteins. Lithium's influence on "traditional" and newly recognized second messenger systems will also be reviewed. Every effort has been made to distil the extent of the new knowledge into a form that will be acceptable to the clinician without being simplistic. It must be appreciated that there is still much to learn in this field and that the future will no doubt bring new discoveries that will make things even more complicated.

Correspondence:
Dr J Segal,Tara Hospital, The H Moross Centre,P Bag X7, Randburg,2125, South Africa
email:joses@iafrica.com

Pharmacodynamics and Pharmacokinetics

Lithium, mined from Spodumene, the lightest of the alkali metals, is not protein bound in human plasma. It undergoes almost no biotransformation and is eliminated almost entirely via renal excretion. Because of the narrow therapeutic index, therapeutic drug monitoring is mandatory and forms the basis of standard clinical practice in all psychiatric units. Therapeutic target ranges vary, but levels of 0,5-1.5 mmol/l are generally adhered to.[14,18,20,21]

Drug monitoring takes the form of trough serum levels about 12 hours after the last oral dose has been administered. Until recently this was thought to be a reasonable method of monitoring compliance and interpreting therapeutic effects. These rather arbitrary values simply represent the levels at which the probability of therapeutic response without intolerable side effects are achieved.[18] The logic, very basically, being something like this:- the amount of lithium in the serum equals the amount of lithium in the central nervous system, equals a given clinical therapeutic and toxic effect. It is now known that such logic is flawed.

Every clinician that has ever prescribed lithium would have first hand knowledge of the fact that for some patients the serum levels of lithium often bare very little relevance to therapeutic effect. Patients seem to improve clinically at serum plasma levels that are unique to each individual. Not surprisingly patients also display a vast range of dosage tolerability in relation to lithium-induced side effects. There is now evidence to show us how and why this should be:

Concentrations: It is now known that different tissues in the body reflect different lithium concentrations when at steady state. This means that cereblospinal fluid (CSF) lithium concentration runs at about a third to a half that of serum.[22] The reasons for this are hypothesised to be due to a differential in the expression of the sodium-lithium counter transport mechanisms that exist in the different organ systems.[18]

Isotopes: Naturally occurring lithium exists in two isotopes: Li-6 and Li-7or ^{6}Li and ^{7}Li, depending on the text one reads.[18] Using Li-7 isotopes and anatomical magnetic resonance imaging (aMRI) it is possible to study the human brain pharmacokinetics of lithium. This involves the relationship between brain lithium concentrations to daily dose and plasma steady state levels with clinical mental state in individual patients.[14,18] Relavent findings are:[14]

- A delayed lithium uptake into the CNS with the brain/serum lithium concentration ratios varying widely from patient to patient with a range of 0.1-1.0.[14,18]
- The ratios fluctuate over the course of hours within individual patients and these ratios only weakly correlate with serum lithium levels.[14,18]
- Substantial inter-individual differences in brain lithium concentrations at similar serum levels.[14,18]
- The brain to serum lithium concentration ratio is age dependent. Although the brain to serum ratios are in fact positively correlated, younger patients (mean age 13.4 yrs) have lower ratios than that of adults.[23] These authors suggest that younger patients need higher plasma serum concentrations than adults to maintain adequate brain concentrations.

The sodium/potassium pump (Na^+,K^+-ATPase): is involved in the control of neuronal excitability. It is also involved in the control and transport of lithium into and out of the neuron and it may be a site of one of the therapeutic effects of lithium. Lithium has been found to decrease the activity and function of the Na^+,K^+-ATPase pump in the CNS and especially in the hippocampus.[17,24] Once again, large inter-individual variation in the activity of this pump has rendered interpretation of these findings difficult.[17]

The inadequacy of our previous understanding is demonstrated through these findings which support in part, the clinically observed delay in lithium's therapeutic effects. They also provide an anatomical substrate for the differential in individual sensitivities to the therapeutic and toxic effects of lithium.

The effects on ion systems

It is now known that both membrane transport systems (eg. Na^+,K^+-ATPase pump) and ion channels (eg. voltage dependant sodium channels and the sodium-calcium exchanger) play roles in regulating the concentration of intracellular lithium.[15] It seems that this effect is on the basis of the transport system accepting the lithium as a substitute for it's normal ionic substrates (like calcium or magnesium). There is also some suggestion that there may be specific membrane transport systems that specifically recognise lithium eg. gradient dependant sodium lithium exchanger.[15,25] There is data that suggests that there are abnormalities in the concentrations of both sodium and calcium ions in the red blood cells of bipolar patients. Lithium appears to reverse these changes, possibly through the direct influence it has on the membrane transport systems mentioned above, especially the Na^+,K^+-ATPase pump. It is unclear whether the pathogenesis of bipolar illness involves dysfunction of these membrane transport systems. There is data to show that there is a direct impact by lithium on concentrations of calcium and sodium ions in the red blood cells of bipolar patients.[17] How these findings relate specifically to human neuronal tissue remains to be elucidated.

The effects on neurotransmitter and neuropeptide systems

The effects of lithium on various neurotransmitters have been studied fairly extensively but results have been difficult to interpret. There has been a recent shift to studying the effects of lithium on the second messenger systems and other intracellular events. Succinctly put:- lithium appears to alter and restore the balance among aberrant neurotransmitter and neuropeptide signalling pathways in the limbic system. The detailed effects of lithium on each neurotransmitter and neuropeptide system is presented in Table 1.[15-17]

The effects of lithium on the neurotransmitter systems are truly ubiquitous. It is also clear that there are still large gaps in our knowledge. Most of all, interpreting the clinically meaningful influences with regard to the therapeutic effects of lithium in bipolar disorder remains an enigma.

Effects on neuronal signal transduction

Signal transduction can be defined as the process by which the binding of neurotransmitters to receptors, located on the extracellular aspect of the neuronal plasma membrane, produces alterations in neuronal functioning.[29] There are numerous methods employed by the neural network to achieve this aim. Some examples include, G proteins, second messenger systems and protein phosphorylation.

Effects on G proteins

G proteins are a family of membrane proteins that are involved in all the transmembrane signalling in the nervous system, bar that occurring by activation of receptors that contain intrinsic ion channels. G proteins are so named because of their ability to bind a group of nucleotides called guanosine triphosphate (GTP) and guanosine diphosphate(GDP).

G protein functions principally to translate extracellular receptor activated signals across the cell membrane, with activativation of various intracellular processes and effector systems.[26,27]

Under basal conditions, G-proteins exist in the cell membrane as heterotrimers composed of a single GDP bound α subunit with a β and γ subunit. With receptor-ligand coupling the GDP is displaced from the α subunit and replaced with GTP which results in uncoupling of the heterotrimeric form into a free GTP bound α monomer and a $\beta\gamma$ subunit. These two separate activated subunits are now free to directly regulate the activity of a number of effector proteins, for example, adenylate cyclase or phospholipase-C. The α subunit degrades the GTP back into GDP with an enzyme called GTPase which completes the cycle.[26]

About 80% of all hormones, neurotransmitters and neuromodulators elicit cellular responses through G proteins. Receptors coupled to G-proteins include those for the catecholamines (dopamine, noradrenaline), serotonin, acetylcholine and various peptides like vasopressin and substance P.[26]

Table 1:Effects of Lithium on the Various Neurotransmitter Systems

Presynaptic Effects	*Inhibitory Receptor Effects*	*Overall Neuro-transmission*	*Postsynaptic Effects*
SEROTONIN			
Increased Release.	Decreased sensitivity of the 5HT1A receptor, leading to a nett increase in 5HT release per impulse.	Increased in the ascending pre-synaptic 5HT system.	Decreased sensitivity of the 5HT1 and 5HT2 receptors.
NORADRENALINE			
1. Increased Release. 2. However returns to baseline with chronic use, possibly via a decrease in Alpha$_2$ sensitivity.	Decreased sensitivity of the Alpha$_2$ receptor.	Increased	1. Prevents BARC super-sensitivity induced by neurotransmitter depletion. 2. BARC increase in CAMP is inhibited.
DOPAMINE			
1. Increase in DA turnover. 2. Decreased DA synthesis	Unknown	Reduced	1. Prevents DA receptor super sensitivity induced by neurotransmitter depletion. 2. D_1 and D_2 effects are unknown. 3. Overall effects are post-receptor (ie, second messenger systems and others). 4. Li prevents HLP induced DA receptor up-regulation.
ACETYLCHOLINE			
Unknown	Unknown	Increased	1. Prevents receptor super-sensitivity induced by neuro-transmitter depletion. 2. Effects on the M2 receptor are mixed.
GABA			
1. Increased GABA levels in the striatum & midbrain. 2. Increased turnover of GABA in the hippocampus and striatum.	Unknown	Increased	Increased $GABA_B$ receptors
GLUTAMATE			
1. Initial decrease in GLU reuptake. 2. Chronic Lithium causes increased GLU reuptake. 3. This is possibly a mechanism responsible for the neuroprotective effects of Li therapy.	Unknown	Increased	1. NMDA mediated increased in IP3 concentration. 2. Decreased intracellular calcium with NMDA receptor activation. 3. These actions may also contribute to the neuroprotective effects of lithium.
NEUROPEPTIDES			
1. Increased levels of dynorphin, Substance P tachykinin, neuropeptide y neurokinin A. 2. Increased mRNA levels of dynorphin & tachykinin, indicating Li's role in the regulation of peptide gene expression. 3. Increased release of opioid peptides as above, possibly by autoreceptor inhibition. 4. CSF levels of peptides unchanged.	Unknown	Increased	1. Effects are unknown 2. Possible decrease in the binding sites of encephalin.

Key: 5HT-serotonin; BARC-beta adrenergic receptor complex; CAMP-cyclic adenosine monophosphate
DA-dopamine; D-dopamine receptor; M-muscarinic cholinergic receptor; Li-lithium; HLP-haloperidol
GABA- gama amino butyric acid; GLU- glutamate; IP3 - inositol triphosphate; Li- lithium.
NMDA- n-methyl-d-aspartate; mRNA - messenger ribonucleic acid; CSF- cerebrospinal fluid.

Various authors have reviewed the effects of lithium on the G protein system and their findings can be summarised as follows:[17,26,27]

- Lithium effects the Adenylate Cyclase (AC) second messenger system by effects on the activating G-protein Gs (Stimulatory G protein type). This seems to be at a level of attenuation of receptor-Gs coupling and of the GTP increases expected in response to agonist binding.
- There is significant evidence for lithium inhibiting the Gi (Inhibitory G protein type) by a mechanism of stabilising the inactive undissociated conformation, ie GDP-bound $\alpha\beta\gamma$ heterotrimeric form[27], possibly via competitive effects with magnesium.[17,26]
- Lithium seems to have tissue specific effects as a result of selective Gi attenuation in various cell lines, eg. lymphocytes compared to platelets. Unfortunately there is some conflicting evidence in the literature and it appears that some of the above effects occur in cultured cell lines but not in rat or monkey brain.[17]
- Lithium may effect the G-proteins of the Phosphoinositide second messenger system (see later) via a lowering of the levels of Gq and G_{11}.[27]
- At a genetic level, lithium seems to influence the expression of G proteins. This influence is by attenuating the production of G protein mRNA in the CNS. There is some evidence that this impact is on the $G\alpha_s$ and on the $G\alpha_{i1}$ and the $G\alpha_{i2}$ subunits of the G protein family. These effects are modest and the physiological significance of these effects remain to be elucidated.[17]
- The present thinking seems to be that the majority of the lithium effects on the G protein family are mediated through what is termed "post translational effects". In short this means that the way in which the G protein reacts to effector coupling and its subsequent influence on the specific second messenger system is modified in some way. The process seems to involve the alteration of the balance of equilibrium in the G protein between the active α-GTP complex subunit and the inactive $\beta\gamma$ subunit.[17,27] The evidence to support this notion has been reviewed in detail by Lennox and Hahn.[17] The following is a summary from their article:
  - Lithium induced ADP ribosylation of the Gi protein subunit results in the shifting of the G protein complex into its inactive undissociated $\alpha\beta\gamma$ heterotrimeric form.
  - This tonic inhibition of the Gi subunit increases basal levels of CAMP.
  - On the other hand however, lithium attenuates receptor-mediated activation of Adenylate Cyclase (AC) through a reduction in Gs subunit coupling. This results in a decrease in the peak levels of stimulus induced CAMP.

The net overall effect of the rather complicated lithium mediated G protein effects outlined above, on receptor mediated signal transduction and amplification in the brain remains to be elucidated. The role of G-proteins in the pathophysiology of bipolar disorder also remains an area of much active research. Unfortunately there are a host of complicating issues in this field of research, some of them illustrated by Manji et al recently.[27] Attempts to explain the dichotomous effects of lithium on CAMP will be discussed later in the text in "making sense of the above".

Effects on second messenger systems

The second messenger systems that will be reviewed here briefly in terms of their relationship with lithium include the Phosphoinositide pathway, the Adenylate Cyclase system, the JAK/STAT system, the MAP-Kinase system and the Arachidonic acid system.

The phosphoinositide (phosphatidylinositol) pathway (PI)

Very briefly, this pathway involves a G-protein (Go, Gq, G_{11}, G_{14}, Gz) linked receptor activation of phospholipase-C (PL-C), which metabolises phosphatidyl inositol into the two second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG).[26] The IP_3 arm of the system then releases intracellular calcium from internal stores which then activates calcium and/or calmodulin dependant protein kinases. The DAG arm of the system results in activation of protein kinase C (PK-C) which has various critical substrates as will be outlined later.[29]

The effects that lithium has on the PI system are well documented.[17,26,27,29] The effects on this system can thus be summarised as follows:

- Lithium is a potent and uncompetitive inhibitor of the intracellular enzyme Inositol Monophosphatase. This enzyme is responsible for the conversion of inositol monophosphate into inositol. Inositol is in limited supply in the brain as it cannot cross the blood brain barrier and thus the brain makes use of recycled intracellular inositol. This situation leads to the generation of the "inositol depletion hypothesis" that was put forward in the late 1980's as the mode of action of lithium as a mood stabilising agent.[28] The hypothesis posited that only the most active neurones in the central nervous system would be affected by lithium as they would be the cells most rapidly depleted of available inositol. This would alter their function to the extent of achieving clinical therapeutic benefits in a relatively selective manner. The "inositol depletion hypothesis" has been called into question.[26] However, as highlighted recently there may be another mechanism to explain the relative selectivity of lithium to more active neural tissue.[17] This hypothesis stems from the findings that there is a dramatic increase in the intracellular concentration of lithium in neuronal dendritic spines occurring via ligand-gated ion channels following a train of action potentials. It is postulated that via this method the more active neural tissue would thus accumulate more intracellular lithium, and hence account for its relative therapeutic specificity.
- Reviews of more recent work have shown that lithium effects are occurring down stream in the PI system, in particular on the DAG arm of the system, on proteins such as Protein Kinase C (PK-C) and it's substrates, a couple of them of critical importance are MARCKS and AP-1.[15,17] MARCKS is myristoylated alanine-rich C kinase and is found in hippocampal cells. The effects shown by chronic lithium treatment on MARCKS is dependant on both inositol levels and G-protein influences on the PI system.[15,17] Only chronic lithium treatment has been shown to dramatically reduce the expression of MARCKS. This reduction persists for some time after the withdrawal of lithium, paralleling our clinical observations of the therapeutic effects of lithium. Further details about the effects on MARCKS and AP-1 will be discussed later in the text.
- It is now also known that the reduction in inositol precedes the clinical therapeutic outcome observed with lithium treatment. This temporal dissociation is thought to be in keeping with the true therapeutic effects of lithium. These are occurring further down stream in the PI pathway, as outlined above, and hence again partly account for the delay seen in the therapeutic benefits of lithium. It seems that the truly therapeutically relevant physiological effects of lithium on the PI system falls beyond a simple reduction in inositol levels.[15,17]

Adenylate cyclase (AC) system

Very briefly, this pathway involves a G-protein (Gs, Gi) linked receptor activation of adenylate cyclase (AC) which catalyses the synthesis of cyclic adenosine monophosphate (CAMP). CAMP then activates protein kinases and other substrate proteins.[26,29]

The effects of lithium on the AC system have also been studied and recently reviewed.[15,16,17] Some of these effects have already been discussed above in the review of the effects of lithium on the G-protein family.

Other significant effects not discussed above include the following:

- Lithium inhibits activation of the AC system. Firstly, this seems to be achieved via inhibitory effects on the activating GTP/GDP cycling in the G-protein complex that occurs with agonist binding as outlined previously and also possibly by lithium's antagonistic effects on Mg^{++}. Secondly, by reducing the expression of PK-C lithium influences the AC system via the "receptor cross talk" effects that occur between the two systems.[17,26]
- The majority of lithium side effects on the thyroid gland and the kidney, namely hypothyroidism and nephrogenic diabetes insipidus, have been postulated to arise from the effects lithium has on thyroid stimulating hormone sensitive AC and antidiuretic hormone (vasopressin) sensitive AC respectively.[15,30]
- The role of the AC second messenger system in the pathogenesis of bipolar disorder, and the lithium induced changes in the treatment thereof remains unclear.

Making sense of the above

Only one author to date has attempted to integrate the above-mentioned effects of lithium on the G protein family and the PI and AC second messenger systems into a coherent whole. Jope has introduced a hypothesis called the "bimodal model" for the effects exerted by lithium.[31] Unlike the unidirectional "inositol depletion hypothesis" the "bimodal model" attempts to explain the documented bi-directional effects of lithium on the second messenger systems as outlined in the text above.

According to this model the contradictory effects of lithium on the levels of CAMP ie. elevation of basal CAMP levels and a decrease in the stimulus induced increase thereof can be conceptualised as being complementary. Specifically if one considers it to represent an attenuation and stabilisation in the overall fluctuation of CAMP levels rather than representing one action having a greater consequence than the other. As CAMP modulates transcription factors that regulate gene expression this stabilisation of CAMP levels should hypothetically at least stabilise the regulated genes in the affected neurones, thus contributing to the therapeutic efficacy of

chronic lithium treatment.[31]

The influence of the bimodal model on the PI system will be dealt with later in the text when we look at AP-1. Overall the bimodal model certainly has its strengths in helping one understand and conceptualise the very complicated influence lithium has on the neuron. Unfortunately some authors have viewed the model as "overly simplistic".[17]

Other second messenger systems

Other second messenger systems of potential importance to psychiatry that have come to light in the last decade or so, are the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) system, the MAP-Kinase system and the Arachidonic Acid systems.

- *The JAK/STAT[32,33] system* is involved in the signal transduction of the cytokines. It controls the cytokine dependent gene expression and cellular survival and development. This system is critical for host defences. The cytokines are generally divided into two families according to the receptor type to which they bind. The Type-1 family include amongst others the interleukins eg. IL-21 and Thymic Stromal Lymphopoietin. The Type 2 family include the interferon's, limitin and other interleukins eg. IL-10. The cytokines are capable of both positive and negative regulation of transynaptic signalling.[32] It is also now known that growth factors can also activate the JAK/STAT cascade.[33] Little data exists on the specific role of the JAK/STAT systems in the CNS. What little there is has been reviewed recently.[33] From this review one realises the following.
  - It appears that glial cells of various types use the JAK/STAT system for a variety of functions, including glial cell survival, the selective promotion of cellular differentiation along glial cell lines rather than neuronal ones, implying a role in the control of brain development.
  - There is also data to support the role of the JAK/STAT system in the control of the inflammatory process in the brain. The function of the molecule nitric oxide (NO) produced by the glial cells in the brain has also been shown to be influenced by the JAK/STAT system. NO is documented to play a role in inflammatory and neurotoxic states, including disease states such as multiple sclerosis, Alzheimer's and Parkinson's diseases. Other disease states thought to be associated with the JAK/STAT systems include human brain tumours and stroke.
  - Finally, in developing and in mature brains, the control of neuronal proliferation, differentiation and survival is thought to be under the control of the JAK/ STAT system.[33]

The role of the JAK/STAT system in bipolar disorder remains to be elucidated. However it's role in depressive disorders has been briefly examined.[34] Later on in the text the role of lithium in neural plasticity is discussed. Many of the effects may be facilitated by the JAK/STAT system.

- *The MAP-Kinase system* (MAP - mitogen activated protein) is involved in the neurotrophic factor regulated signal transduction pathway and the neurotrophic factor dependant gene expression.[35] The neurotrophins that activate this system include trophic factors such as nerve growth factor (NGF),

brain derived neurotrophic factor (BDNF) and the neurotrophin family eg, NT-3 and NT-4. These neurotrophic factors activate

a receptor complex known as Trk. Various types exist, eg. Trk-A and Trk-B. Activation of these receptors results in a cascade that culminates in the phosphorylation of various substrated proteins, amongst them a protein called MAP. Importantly it has been shown that there is cross talk between the neurotrophic factor activated messenger systems (MAP-Kinase) and those activated by the classical neurotransmitter systems. The nett effects of this remain to be elucidated. Overall the MAP-Kinase system is thought to be involved in neuronal development, differentiation and survival and plays a role in neuronal signalling processes as well.[35]

The role of the MAP-Kinase system in bipolar disorder is unclear. The role of this system in depressive disorders and in the function of antidepressant medications has been reviewed recently.[34] There is a little data on the effects of lithium on the MAP-Kinase system.[19] It seems that lithium may modulate gene expression in the CNS via interaction with a transcription system initiated by activator protein-1 complex (Ap-1). It seems that the impact lithium has on Ap-1, may in part, be driven by its influence on the MAP-Kinase system. There is however data to show the role of this system in the neurotrophic and neuroprotective actions of the mood stabiliser valproate in bipolar disorder.[36]

- *The Arachidonic Acid system* has recently emerged as yet another second messenger system that seems to have a role in psychiatry.[37] Arachidonic acid is a polyunsaturated fatty acid and forms part of a second messenger system that is involved in a whole host of neuronal processes. These include the modulation of ion channels, neurotransmitter uptake and trans-synaptic neurotransmission.[35] Crucially it is also involved in cell growth, apoptosis[38] and the inflammatory process in the central nervous system in general.[39] The arachidonic acid system is responsible for the production of the Eicosanoids, which include the prostaglandins, thromboxanes, the leukotrienes and the dihydroxyeicosatrienoates. Activation of the arachidonic acid pathway can be precipitated by a whole host of stimuli, including inflammatory, immunological, neural, chemical or mechanical factors. Prostaglandins have profound effects on the inflammatory process and the leukotrienes are important components of the anaphylactic process.[39] Rapoport and Bosetti have provided us with data on the role of lithium in the arachidonic acid system, including the following:[37]
  - Lithium reduces the turnover of arachidonic acid in the rat brain by 75% with long-term treatment in a highly specific manner, without much effect on other polyunsaturated fatty acids.
  - This reduction is associated with reduced arachidonoyl-coenzyme A, reduced messenger RNA, and reductions in protein and cytosolic phopholipase A_2 type IV.
  - Lithium has also been shown to decrease the protein level and activity of the enzyme cyclooxygenase 2 (COX-2), as well as the concentration of prostaglandin E_2, which is a metabolite of arachidonic acid metabolism by COX-2.

In this paper the authors point out that there are other lines of evidence that support the role of lithium as an inhibitor of the arachidonic acid pathway and why this pathway is disturbed in bipolar disorder.[37] In particular they cite the following:

- neuro-protective effects that lithium has on cerebral infarction and inflammation in animal models.
- The beneficial effects of n-3 poly unsaturated fatty acids have in the treatment of mania.
- The role of the prostaglandins D_2 and E_2 in the sleep wake circadian rhythm disturbances seen in bipolar illness.

These authors also point out that the anticonvulsant drugs sodium valproate and topiramate also perform a number of similar functions to lithium, namely decrease arachidonic acid levels and are neuro-protective respectively.[37]

These second messenger systems are the focus of enormous research activity.[32] To date there is little specific data examining these systems in psychiatric diseases. There is also little data on the specific effects of psychiatric medications on these systems. However as these systems are indeed involved in gene transcription, survival and differentiation of cell types including neural tissue and control of inflammatory responses, there is little doubt that in due course these systems will be securely linked to psychiatric illness of one type or another.

By way of example, Duman et al recently gave us insights into the role the JAK/STAT and MAP-Kinase systems play and how they fit into the "grand scheme" of our understanding of the pathophysiology of depression and addiction.[34] What is clear from their article and others like it, is the intimate role neuronal atrophy and cell death play in the pathophysiology of mental illness and the protective effects antidepressants and lithium play.[19,34] It seems to be simply a matter of time before lithium and other drugs are examined in these systems and their effects and impact on mental disorders such as bipolar illness more clearly understood.

This new data opens up an entire new field of research on the mechanisms of action of lithium and other mood stabilising compounds in bipolar disorder. It also offers us the theoretical framework for new candidate drugs like the COX-2 inhibitors as potential anti-manic agents.[37] No doubt this will also result in a significant shift in our understanding of the pathophysiological mechanisms underlying the mood disorder disease process itself. One conclusion that can already be hinted at is the emerging role of the inflammatory process in psychiatric disorders.

Conclusion

In part one of this review we have seen the facts behind the clinically observed individual tolerance and clinical response to lithium. We can now also understand the complicating role of the marked inter-individual variations in the activity of the sodium/potassium pump and other membrane transport systems. We can now recognise the ubiquitous influence lithium has on the various neurotransmitter systems and the many unknown variables that still plague our understanding. The diverse effects that lithium has on the various subtypes of G-protein and second messenger systems can now be understood to be cardinal to its influence on neuronal signal transduction and thus probably to the therapeutic benefits. New roles for lithium in emerging and diverse second messenger systems has opened up an entirely new field of research and has profound implications in the neurobiology of bipolar disorder, implicating the inflammatory response, neuronal atrophy and death. Again there

are a multitude of unknown variables that undermine our understanding. There is also an expanding body of evidence that supports the neuroprotective role of lithium in the human brain, more of which will be presented in part two of this review. It may be that a fundamental shift in our understanding of the pathophysiology of bipolar illness and the therapeutic mechanism of action of lithium is warranted. As more evidence comes to light in the future, this will surely prove to be the case.

Acknowledgements

The author wishes to thank Drs Simon Rubidge and Jaco du Toit for their help and encouragement in the preparation of this manuscript.

References

1. *Thomas J, Reddy B. The Treatment of Mania: A Retrospective Evaluation of the Effects of Electroconvulsive Therapy, Chlorpromazine and Lithium. J Affect Disord 1982; 4: 85-92.*
2. *Lerer B, Moore N, Meyendorff E, et al. Carbamazepine versus lithium in mania: a double-blind study. J Clin Psychiatry 1987; 48: 89-93.*
3. *Lusznot RM, Murphy DP, Nann CM. Carbamazepine vs Lithium in the Treatment and Prophylaxis of Mania. Br J Psychiatry 1988; 153: 198-204.*
4. *Okuma T, Yamashita I, Takahashi R, et al. Comparison of the Antimanic Efficacy of Carbamazepine and Lithium Carbonate by Double-Blind Controlled Study. Pharmacopsychiatry 1990; 23: 143-150.*
5. *Small J G, Klopper M H, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. Arch Gen Psychiatry 1991; 48: 915-921.*
6. *Freeman TW, Clothier JL, Pazzaglia P et al. A Double-Blind Comparison of Valproate and Lithium in the Treatment of Acute Mania. Am J Psychiatry 1992; 149: 108-111.*
7. *Bowden CL, Brugger AM, Swann AC et al. Efficacy of Divalproex, Lithium and Placebo in the Treatment of Mania. JAMA 1994; 271: 918–924.*
8. *Emilien G, Maloteaux JM, Seghers A, et al. Lithium Compared to Valproic Acid and Carbamazepine in the Treatment of Mania: A Statistical Meta-Analysis. Eur Neuropsychopharmacol 1996; 6: 245-252.*
9. *McIntyre RS, Mancini DA, Parikh S, Kennedy S H. Lithium Revisited. Can J Psychiatry 2001; 46: 322-327.*
10. *Gustcott R, Taylor L (1994) Lithium Prophylaxis in Recurrent Affective Illness: Efficacy, Effectiveness and Efficiency. British Journal of Psychiatry 164: 741-746.*
11. *Abou-Saleh M. (1982) Lithium. In: Paykel E, editor. Handbook of Affective Disorders. Edinburgh: Churchill Livingstone, 369.*
12. *Cookson J (1997) Lithium: Balancing Risks and Benefits. Br J Psychiatry 171: 120-124.*
13. *Moncrieff J (1997) Lithium: Evidence Reconsidered. Br J Psychiatry 171: 113-119.*
14. *Kilts CD. The ups and downs of oral lithium dosing. J Clin Psychiatry 1998; 58[suppl 6]: 21-26.*
15. *Lenox RH, McNamara RK, Papke RL, Manji HK. Neurobiology of Lithium. An update. J Clin Psychiatry 1998; 59 [suppl 6]: 37-47.*
16. *Jope RS. Anti-bipolar therapy: mechanism of action of lithium. Mol Psychiatry 1999; 4: 117-128.*
17. *Lenox RH, Chang-Gyu Hahn. Overview of the Mechanism of Action of Lithium in the Brain: Fifty-Year Update. J Clin Psychiatry 2000; 61[suppl 9]: 5-15.*
18. *Kilts CD. In Vivo Imaging of the Pharmacodynamics and Pharmacokinetics of Lithium. J Clin Psychiatry 2000; 61 [suppl 9]: 41-46.*
19. *Manji HK, Moore GJ, Guang Chen. Lithium Up-Regulates the Cytoprotective Protein Bcl-2 in the CNS in Vivo: A Role for Neurotrophic and Neuroprotective Effects in Manic Depressive Illness. J Clin Psychiatry 2000; 61 [suppl 9]: 82-96.*
20. *Hyman SE, Arana GW, Rosenbaum JF Lithium. In: Handbook of psychiatric drug therapy. Third edition: Little Brown and Company, Boston Massachusetts, 1995: 93-123.*
21. *Bernstein Jerrold G. Handbook of Drug Therapy in Psychiatry. Third Edition: Mosby - Year Book Inc. St. Louis Missouri, 1995: 212-228.*
22. *Ward ME, Musa MN, Bailey L. Clinical pharmacokinetics of lithium. J Clin Pharmacol 1994; 34: 280-285.*
23. *Moore CM, Demopulos CM, Henry ME, Steingard RJ, Zamvil L, Katic A et al. Brain to serum lithium ratio and age: An in vivo magnetic resonance spectroscopy study. Am J Psychiatry 2002; 159(7): 1240-2.*
24. *Swann AC, Marini JL, Sheard MH, et al. Effects of chronic dietary lithium on activity and regulation of [Na+,K+]-adenosine triphosphatase in rat brain. Biochem Pharmacol 1980; 29: 2819-2823.*
25. *Sarkadi B, Alifimoff JK, Gunn RB et al. Kinetics and stoichiometry of Na-dependent Li transport in human red blood cells. J Gen Physiol 1978; 72: 249-265.*
26. *Manji HK. G Proteins: Implications for Psychiatry. American Journal of Psychiatry 1992; 149: 746-760.*
27. *Manji HK, Chen G, Shimon H, Hsiao JK, Potter WZ, Belmaker RH. Guanine Nucleotide-Binding Proteins in Bipolar Affective Disorder: Effects of long-term lithium treatment. Arch Gen Psychiatry 1995; 52:135-144.*
28. *Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. Cell 1989; 59: 411-419.*
29. *Hyman SE, Nestler EJ. Overview of Synaptic Neurotransmission. In: The Molecular Foundations of Psychiatry. First edition, American Psychiatric Press Inc. Washington DC. 1993: 23-54.*
30. *El-Mallakh RS. Lithium: Actions and Mechanisms. American Psychiatric Press Inc. Washington DC 1996.*
31. *Jope RS. A bimodal model of the mechanism of action of lithium. Molecular Psychiatry 1999; 4: 21-25.*
32. *O'Shea JJ, Gadina M, Schreiber RD. Cytokine signaling in 2002: New surprises in the Jak/Stat Pathway. Cell 2002; 109: S121-S131.*
33. *Dell'Albani P, Santangelo R, Torrisi L, Nicoletti VG, Giufrida Stella AM. Role of the JAK/STAT Signal Transduction Pathway in the regulation of gene expression in the CNS. Neurochemical Research 2003; 28: 53-64.*
34. *Duman RS, Heninger GR, Nestler EJ. A Molecular and Cellular Theory of Depression. Arch Gen Psychiatry 1997; 54: 597-606.*
35. *Hyman SE, Nestler EJ. Initiation and Adaptation: A Paradigm for Understanding Psychotropic Drug Action. Am J Psychiatry 1996; 153: 151-162.*
36. *Manji HK, Moore GJ, Chen G. Clinical and Preclinical Evidence for the Neurotrophic Effects of Mood Stabilizers: Implications for the Pathophysiology and Treatment of Manic-Depressive Illness. Biol Psychiatry 2000; 48: 740-754.*
37. *Rapoport SI, Bosetti F. Do Lithium and Anticonvulsants Target the Brain Arachidonic Acid Cascade in bipolar Disorder? Arch Gen Psychiatry 2002; 59:592-596.*
38. *Surette ME, Fonteh AN, Bernachez C et al. Perturbations in the control of cellular arachidonate levels block cell growth and induce apoptosis in HL-60 cells. Carcinogenesis 1999; 20: 757-763.*
39. *American Academy of Ophthalmology (1997-1998) Fundamentals and Principles of Ophthalmology: Basic and Clinical Science Course, Section 2. Beach St 655, San Francisco, CA. 317-319.*
40. *Hyman SE, Nestler EJ. Mechanisms of Neural Plasticity. In: The Molecular Foundations of Psychiatry. First edition, American Psychiatric Press, Inc. Washington DC. 1993; 95-122.*

Lithium: Priming the next 50 years

Brian H Harvey
Division of Pharmacology, School of Pharmacy, North-West University, Potchefstroom,South Africa

Lithium salts are alumni of "the class of the 1950's", a period of unprecedented excitement and discovery in psychotropic drug development. However, drugs such as chlorpromazine and imipramine, as well as lithium salts, were for the most part fortuitous discoveries, and not a product of innovative drug design. Recent years has seen a concerted effort to understand the neurobiology of affective illness, as well as psychotropic drug action, with the introduction of new generation neuroleptics and antidepressants. Lithium, however, remains a law unto itself.

Lithium salts remain a drug of choice in the treatment of bipolar disorder. Their unique ability to "stabilize" mood, as opposed to the mood-selective actions of the neuroleptics and antidepressants, has intrigued researchers and clinicians alike. Further, its simple molecular structure suggests that it has pharmacokinetic and pharmacodynamic differences that in some way set it apart from more complex laboratory synthesized compounds. Then, as eloquently laid out by Dr Segal in his review, the ephemeral pharmacodynamic nature of lithium can become a life-long obsession as researchers strive to fully understand its mechanism of action. It is these attributes that have hinted that lithium may provide a means to understanding the complex pathobiology of affective illness and, indeed, how mood is regulated at the molecular level.

Because of this, much of the discovery pertaining to the mechanism of action of lithium has always been regarded as an important contribution. In the seventies, the action of lithium on the adenylate cyclase-cAMP system was instrumental in linking drug action to sub-cellular effector mechanisms and today the cAMP cascade, and its activation of down-stream effector molecules, such as protein kinase A and cAMP responsive element binding protein (CREB), is recognized as a critical link in understanding psychotropic drug action.[1] Later, during the eighties with the unraveling of the phosphoinositide pathway, and the actions of lithium thereon, great expectation was placed on the "inositol depletion hypothesis" to explain the dual action of lithium as a mood stabilizer. This hypothesis has since enjoyed new emphasis in recent years with the demonstration of the pharmacological and behavioral actions of myo-inositol, as well as the efficacy of high-dose myo-inositol in anxiety disorders.[2] However, as has been described in Dr Segal's review, the mode of action of lithium seems far more complex than our hypotheses. Certainly we now know that selectivity for an extra-cellular receptor does not imply selectivity in the sub-cellular domain. Thus, receptors and their sub-cellular signal transduction mechanisms communicate with one another on an on-going and dynamic basis, constantly striving to maintain optimum neuronal function and homeostasis .[3] By implication, this suggests that actions on the putative neurobiological targets described in Segal's review may or may not be inter-linked into a response that is dependent on a single neurobiological target. Whether this is so and the identity of such a target, however, remains illusive.

One of the more significant discoveries in the late 1990's was the seminal discovery of lithium's inhibitory action of glycogen synthase kinase (GSK) 3b and its effect on cellular and neuronal development.[4] GSK-3b has a pivotal role in cell survival and this observation paved the way for the pioneering work by Manji and colleagues in elucidating the putative neuroprotective action of lithium and its possible clinical relevance.[5,6,7] Considering recent evidence that mood disorders are associated with neuronal atrophy and loss of glial cells[8], the action of lithium on cellular resilience may have particular relevance. This not only has implications for mood disorders, but has also opened the way for the possible use of lithium in neurodegenerative disorders such as acquired immune deficiency syndrome (AIDS)-related dementia[9], Alzheimer's disease[10] and Huntington's disease .[11]

Another neuromodulator that has realized a great deal of attention over the past decade, and which lithium also modulates, is the nitric oxide (NO)-cyclic-GMP pathway.[12,13] NO mediates cross-talk between various neurotransmitter systems, and also plays a regulatory role in neuron survival and possibly in determining the outcome of psychotropic treatment.[14]

The review by Segal is an ideal primer for those clinicians seeking a deeper understanding of how lithium may exert its therapeutic effects. Although our knowledge of lithium's varied actions is impressive, it would appear that this small earth metal is to remain an enigma far into the new millennium, challenging our thinking but, at the same time, expanding our horizons.

Correspondence:
Professor BH Harvey,Division of Pharmacology, School of Pharmacy, North-West University, Potchefstroom,2520,South Africa
email: fklbhh@puknet.puk.ac.za

References

1. *D'Sa C, Duman RS. Antidepressants and neuroplasticity. Bipolar Disord 2002; 4: 184-194.*
2. *Harvey BH, Brink CB, Seedat S, Stein DJ. Defining the neuro-molecular action of myo-inositol: Application to obsessive-compulsive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry 2002; 26: 21-32.*
3. *Harvey BH. The neurobiology and pharmacology of depression: A comparative overview of serotonin-selective anti-depressants. S Afr Med 1997; J 87, 540-552.*
4. *Klein PS, Melton DA. A molecular mechanism for the action of lithum on development. Proc Natl Acad Sci USA 1996; 93: 8455-8459.*
5. *Manji HK, Moore GJ, Chen G: Lithium upregulates the cytoprotective protein bcl-2 in vitro and in the CNS in vivo: a role for neurotrophic and neuroprotective effects in manic-depressive illness J Clin Psychiatry 2000; 61(supp9): 82-96.*
6. *Moore GJ, Bebchuck JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. The Lancet 2000; 356: 1241-1242.*
7. *Moore GJ, Bebchuk JM, Hasanat K, et al. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl's neurotrophic effects? Biol Psychiatry 2000; 48: 1-8.*
8. *Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry 2000; 48: 766-777.*
9. *Harvey BH, Meyer CL, Gallicchio VS, Manji HS. Lithium salts in AIDS and AIDS-related dementia. Psychopharmacol Bull 2002; 36: 5-26.*
10. *Alvarez G, Munoz-Montano JR, Satrustegui J, Avila J, Bogonez E, Diaz-Nido J. Regulation of tau phosphorylation and protection against beta-amyloid-induced neurodegeneration by lithium. Possible implications for Alzheimer's disease. Bipolar Disord 2002; 4:153-65*
11. *Senatorov VV, Ren M, Kanai H, Wei H, Chuang DM. Short-term lithium treatment promotes neuronal survival and proliferation in rat striatum infused with quinolinic acid, an excitotoxic model of Huntington's disease. Mol Psychiatry 2003 Dec 31 [Epub ahead of print].*
12. *Harvey BH. Affective disorders and nitric oxide: A role in pathways to relapse and refractoriness. Hum Psychopharmacol 1996; 11, 309-319.*
13. *McLeod TM, Lopez-Figueroa AL, Lopez-Figueroa MO. Nitric oxide, stress, and depression. Psychopharmacol Bull 2001; 35: 24-41.*
14. *Harvey BH, McEwen BS, Stein DJ. Neurobiology of antidepressant withdrawal: Implications for the longitudinal outcome of depression. Biol Psychiatry 2003; 54: 1105-1117.*