Lithium- an update on the mechanisms of action

Part two: neural effects and neuroanatomical substrate

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Abstract
Lithium has been clinically utilized for about 50 years. It is only in the last several years however that there has 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.This, the second of a two part review will focus principally on neural effects and neuroanatomical substrates.

Key words: *Lithium, Neural, Neuroanatomical, Substrate, Bipolar*

This article is the second of a two part review of the mechanisms of action of lithium. Part one of this review appeared in Vol7 No2, May 2004 issue of this Journal.

In part one of this review the pharmacological principles behind lithium's therapeutic effects were detailed along with the impact it has on signal transduction, including the multitude of ionic and neurotransmitter effects and the impact on G proteins. Lithium's influence on "traditional" and newly recognized second messenger systems was also discussed. It is clear that our understanding of the mechanisms of action of lithium have been increasing rapidly over the last several years. Very detailed and complicated review articles have been published.[1-6] In this second part we will focus our attention on the new data emerging on the profound role lithium has in influencing neuronal functions, ranging from gene expression to neuroprotective and neurotrophic effects, as well as the potential neuroanatomical substrates of bipolar disorder.

Effects on gene expression

Regulation of gene expression is a vastly complicated subject and an overview of the topic falls way outside of the scope of this text. Data linking lithium to the alteration of neuronal gene expression is to date reasonably sparse, but it is increasing steadily. Thus far a number of studies have demonstrated lithium effects on a number of the various steps towards the activation of gene expression. Two methods of gene expression regulation that have thus far been implicated with lithium are the activator protein-1 complex or AP-1, and cyclic adenosine monophosphate response element or CRE.

Activator protein-1 (AP-1)

The AP-1 transcription factor complex works with the help of immediate early gene transcription factors in particular c-Fos and c-Jun. AP-1 is activated by protein kinase C via the phosphoinositide (phosphatidylinositol) pathway (PI) second messenger signal transduction pathway and possibly via the influences of the MAP-Kinase system as well.6 Gene transcription proceeds when AP-1 binds to its DNA site called tetradecanoylphorbol acetate response element or TRE.[6,7]

Cyclic adenosine monophosphate response element (CRE)

CRE's are activated by a family of transcription factors called cyclic adenosine monophosphate response element binding proteins or CREB proteins. These CREB proteins are activated via the Adenylate Cyclase/CAMP second messenger systems. Gene transcription proceeds when the CREBs activate CRE in the regulatory domain of the DNA sequence.[7]

The evidence for the effects of lithium on gene expression has been fairly extensively reviewed,[1,2,4-6,8] from which we learn the following:

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- *Regarding the AP-1 system of gene expression*
  - Lithium increases the expression of the transcription factors c-Fos and c-Jun.
  - Lithium increases the basal unstimulated (via receptor agonist binding) binding activity of AP-1 to TRE.
  - Chronic lithium treatment has been shown to increase the genetic transcription of proteins known to be regulated by AP-1.
  - Dichotomously though, lithium decreases the binding activity of AP-1 when it is induced by a receptor binding stimulus.

These contradictory findings have been explained as representing a differential effect that lithium has on various neurons depending on the level of their activity.[4] Lithium thus seems to increase AP-1 activity at the basal level but decreases it when the neurons are stimulated.[2,3] It is extremely interesting and perhaps not surprising to learn that valproic acid, who's mood stabilizing properties rivals that of lithium, appears to function in a similar fashion.[9] The bimodal hypothesis mentioned earlier is a model that attempts to explain these dichotomous observations on AP-1. This model shows that because lithium both increases the basal levels of AP-1 and diminishes the stimulated highest peak level activity, the net effect is an overall stabilisation and minimization in the magnitude of signal fluctuations at the level of gene expression.[3]

- *Regarding the CRE system of gene expression*
  - Lithium has been shown to modulate these transcription factors.[2]
  - Lithium also has been shown to increase levels of CREB.[4]

A pertinent question relates to the target genes responsible for the therapeutic benefits of lithium and the pathophysiology of bipolar illness. As there are 10,000 to 15,000 genes expressed in a given cell at any one time, isolating the changes in gene expression as a result of drug treatment is going to be a very complicated business, requiring novel research methodologies.[6,10]

The genetic targets for lithium

Despite the complexities mentioned above there is some emerging data showing us which genes lithium targets specifically. I will very briefly mention one of them here.

- The transcription factor PEBP2β (polyoma enhancer binding protein 2β) is one of the genes identified thus far to have markedly increased expression and functioning following lithium treatment. This increased expression results in a dramatic increase in the levels of a neuroprotective protein called B-cell lymphoma/leukaemia-2 (bcl-2). These increases have been seen predominantly in areas such as the frontal cortex, hippocampus and the striatum.[4,6,10]

The protein bcl-2 is considered to be a neural "protector" by virtue of its ability to inhibit neural cell death by apoptosis and necrosis precipitated by numerous noxious stimuli. It also promotes neurite sprouting and influences the genetic control of axon growth. It is localized on the outer membranes of the mitochondrion, endoplasmic reticulum and nuclear membrane and seems to have multiple protective mechanisms of action including antioxidant effects, enhancement of mitochondrial reuptake of intracellular calcium and attenuation of the release of calcium from the mitochondrion amongst others.[6,10] Valproate appears to also increase the levels of bcl-2.[6,11]

The detail of the significance of these findings regarding bcl-2 has been reviewed extensively.[6,10] The following summary extracted from the review by Manji et al gives a brief overview of the multitude of neuroprotective effects of bcl-2[10]:-

- Protects against lethal effects of a variety of reactive oxygen species.
- Protects against growth factor deprivation.
- Protects against effects of ionising radiation.
- Protects against glucocorticoid toxicity
- Reduces neuropathology after focal ischemia
- Reduces neuropathology after traumatic brain injury
- Reduces axonomy induced motor neuron death
- Promotes regeneration of axons in the mammalian CNS

Bcl-2 is thus crucial to any neuroprotective effects noted in the central nervous system and its interaction with lithium will be discussed in detail below.

Effects on neural plasticity

Key authors have reviewed this fascinating topic.[1,4,6,10] It is highly technical and extremely complicated but the following is a user-friendly extract from these articles. To discuss the effects of lithium on neural plasticity we need to have some understanding of Glycogen Synthase Kinase –3β (GSK-3β).

GSK-3β seems to be a double-edged sword in the human central nervous system. It is a kinase known to play a crucial role on the one hand in regulating the pattern and course of embryonic and adult neural development in mammals (and many other lesser organisms). GSK-3β is also important in a host of neural functions, but in particular the phosphorylation of intracellular proteins involved in the cytoskeletal modelling and growth of neural tissue, like c-jun, tau and β-catenin and other microtubule associated proteins like MAP-1B and synapsin I.

On the other hand GSK-3β also negatively influences and inhibits another novel signal transduction system with the name of Wnt. GSK-3β influences this Wnt system by effects on β-catenin. Both β-catenin and tau have been implicated in certain types of neuronal cell death and GSK-3β itself has been shown to induce neuronal changes consistent with apoptosis under certain conditions.

Lithium (and not surprisingly, valproate) is a potent inhibitor of GSK-3β. As a result it has significant effects on the expression of β-catenin. At this time the full clinical relevance of this is unknown however it is strongly suggested to be crucial in the neuroprotective effects of lithium. It is also considered to be the basis on which lithium is capable of influencing neural genetic transcription and thus growth with long-term use. Lithium also inhibits the phosphorylation of tau, MAP-1β and as discussed in partone of this review it significantly reduces the expression of myristoylated alanine-rich C kinase (MARCKS) which is intimately involved in the neural remodelling process by its ability to bind

and cross link actin. The actin cytoskeleton is crucial in the neuronal activities of morphogenesis and secretion. It is thus clear that MARCKS is crucial in neuronal growth and brain development. The lithium induced reduction in the expression of MARCKS appears to be shared by Valproate. This lithium induced down regulation of MARCKS expression may play a role in altering synaptic membrane structure in such a way as to facilitate the stabilization of aberrant neuronal activity in key brain regions.[4] Overall it seems that lithium (and valproate)[11] has effects that influence neuroplastic changes in processes associated with receptor signal transduction and neurotransmitter release.

The neuroprotective and neurotrophic effects

Detailed reviews[4,6,10,12] by a number of the worlds leading authorities in this field have shown that there is significant of evidence to support the role of lithium and valproate as neuroprotective and neurotrophic agents in the human brain. The data is complex and intricate and so I will simply put forward here a distillation of the common findings of the above review articles.

The majority of the neuroprotective and neurotrophic effects of lithium appear to occur through its influences on two main role players, bcl-2 and GSK-3β. As outlined previously lithium treatment results in increased levels of bcl-2 and inhibition of GSK-3β in neuronal tissue. The net effect of these changes seems to afford lithium significant neuroprotective and neurotrophic properties.

These theoretical models have been clinically confirmed in humans.[6,10,12,13] In order to understand the evidence we need to discuss N-Acetyl Aspartate.

N-Acetyl Aspartate (NAA)

NAA is an amino acid who's functional role in the human CNS has not been fully elucidated yet.[11-14] It is considered to be localised exclusively to mature neurones. It is not found in other brain cells like glia, or in CSF or blood. NAA is deemed to be a marker of neuronal viability and function. Abnormally low levels of NAA in CNS diseases like amyotrophic lateral sclerosis, mitochondrial encephalopathies and HIV dementia have been shown to normalise with remission of the CNS symptoms.[12]

Lithium treatment has been shown to increase levels of NAA in rodent brain, human neuronal cells in culture and in vivo in human bipolar patients and healthy volunteers.[12]

The in vivo studies using quantitative proton magnetic resonance spectroscopy make fascinating reading and are essential study material for the biological enthusiast.[12,13]

The lithium induced increases in NAA seem to occur mainly in the frontal and temporal lobes. Interestingly there was no correlation between the increase in NAA and the lithium levels. The implications of this finding was not specifically addressed by the authors.[12] However one can speculate that this finding is consistent with the comments made about the pharmacodynamics and pharmacokinetics of lithium earlier on in this review. One cant help but postulate that the clinical response one gets with lithium in certain individual patients may be explained by the rise in NAA which seems to be independent of lithium levels rather that the absolute level of serum lithium. Further study is needed to clarify this situation.

The neuroanatomical substrates of bipolar mood disorder

There are early and tentative suggestions in the literature that biologists are starting to narrow down the anatomical substrate of bipolar disorder. Most of the findings exist in animal models. A recent review of the data seems to suggest that the following anatomical structures are the key role players[5]:-

- Anterior cingulate cortex.
- The nucleus accumbens.
- Ventral striatal and paralimbic brain regions.

Lithium induced effects in rodent models suggest that lithium's activity is predominantly confined to the left frontal lobe, with alteration in neural processing in the paralimbic-frontal-striatal pathways. These findings are supported by a decrease in immediate early gene expression in the frontal cortex and an increased density of frontal-cortical serotonin transporters.[5] Brain regions that have been implicated in studies with humans are consistent with the above.[12] These findings seem to be consistent on the whole with the lithium induced increases of NAA levels outlined above.

Summary

There is now data indicating that lithium influences almost every step in the complicated path of neuronal signal transduction. This ranges from neurotransmitter production right through to the end point of gene expression and ultimately the shape, function and even protection of certain neuronal populations involved in the pathophysiology of bipolar illness.

Jope[2] has produced a summary worth committing to memory:-

- Lithium adjusts neurotransmitter balances.
- Lithium adjusts basal and/or stimulated fluctuations in second messenger systems.
- Lithium adjusts basal and/or stimulated fluctuations in transcription factors.
- Lithium modulates expression of specific genes.
- Lithium protects neurons from toxic insults.
- Lithium modifies cytoskeletal function.

Conclusion

Although there has been recent debate regarding the efficacy of lithium, the weight of evidence strongly supports its use as the standard or first-line treatment for acute mania, especially for the euphoric type. In recent years there has seen an explosion of data relating to the mechanisms of action of lithium which has also shed some light onto the possible pathophysiology of bipolar illness. It is now clear that lithium has modulatory effects on a multitude of neural functions. These effects influence neural transmission and signal transduction, gene expression and neuronal plasticity. Newly identified actions of lithium include neural protection from a host of noxious stimuli and enhancement of neural growth. It is currently unknown which of these effects are crucial for the therapeutic effects of lithium in bipolar disorder. Further study is also still needed to elucidate the potential for a new role for lithium in the treatment of neurodegenerative conditions.

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Lithium mechanism: Improves insight into bipolar disorder management

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Lithium is a widely prescribed mood stabilizing agent used in the treatment of acute mood disorders as well as the long-term prophylaxis of bipolar disorder (BD). Elucidation of the precise mechanism of action of the drug seeks to improve pharmacological management of BD, and could also provide insight into the pathophysiology of this debilitating illness. Although the mechanisms underlying the therapeutic action of lithium remain poorly understood, recent studies have implicated certain critical pathways as being integral to the effects of the drug, and thus important in the pathophysiology and treatment of BD.

In the preceding article on the neural effects of lithium, Dr Segal summarizes our current understanding of the molecular and cellular actions of the drug. From his detailed review it is apparent that lithium has multiple sites of action that contribute to its therapeutic effects. This is not surprising, since BD has a complex etiology that is likely to involve numerous genes in addition to non-genetic influences. We have yet to identify the genes, both for suscepti-

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bility and protection, which drive the underlying neurobiology of this disorder; thus specific, gene-targeted pharmacology remains elusive. In its absence, diligent scrutiny of the pathways affected by successful mood stabilizers will bring us closer to an understanding of the primary and adaptive neurobiological processes involved in the recurrent mood disorders.

The characteristic delay in response to therapy in manic patients treated with lithium has led to the proposal that the clinical effect requires changes in gene expression. Dr Segal's review of the research into gene effects of lithium is comprehensive. Lithium adjusts signaling activities regulating second messengers, transcription factors and expression of a large number of genes. Emerging evidence of the broad influence that lithium exerts in the brain, from ion channels in the membrane, gene expression in the nucleus and even to overall changes in the balance within and between nuclei, emphasizes the reasons that lithium has been the mainstay of BD treatment for over 50 years. The range of its effects on complex interactive neuronal networks is highlighted by the clinical evidence that lithium restores balance to the extremes of the mood spectrum. The efficacy of the drug in the management of both mania and depression has been attributed to two principal effects, namely a reduction in apoptotic activity and an increase in neural plasticity.

The clinical value of this neuroprotection has yet to be fully explored. Lithium is now being considered as a potential therapy for neurodegenerative diseases, since the drug inhibits tau phosphorylation through inhibition of glycogen synthase kinase-3β (GSK-3β).[1] It also has immunostimulant and antimicrobial properties through its suppressive effects on brain prostaglandins and arachadonic acid turnover.[2] The limiting factors in expansion of its use for other applications remain the narrow therapeutic window and incidence of adverse events (which may not occur with the use of other available neuroprotective agents).

In his review, Dr Segal documents the gene events linked to lithium's ability to enhance neural plasticity. Despite in vitro evidence that lithium increases neural plasticity, clinical experience has shown that there are presentations of BD in which lithium therapy has poor efficacy. Patients who either begin their illness with a pattern of rapid cycling (four or more episodes a year) or who progressively evolve this faster pattern tend to be resistant to treatment with lithium.[3] Also, patients who have been well maintained on lithium prophylaxis and then discontinue their medication frequently experience a relapse, and then fail to respond to the reinstitution of lithium at the same or higher dosage.[4] In these instances it seems that the multimodal action of lithium is insufficient to contain the increasingly disordered neurobiology. Combination of lithium with carbamazepine[5], valproate[6] or lamotrigine[7] increases treatment success, perhaps through convergence of their multiple targets of action. Although there is a lack of controlled clinical trials, topiramate, zonisamide and levetiracetam have all been used to boost efficacy in therapy-resistant patients.[5] Interestingly, the addition of the L-type calcium channel antagonist nimodipine has also proved effective in ameliorating mood swings in patients with ultrafast mood oscillations.[8] This gives rise to speculation on the role of calcium dysregulation in the pathophysiology of ultradian cycling.

Clarification of the influence of lithium on molecular targets has prompted research into the development of new mood stabilizers. Promising areas for investigation include agents that inhibit GSK-3β9 and agents that increase expression of brain derived neurotrophic factor (BDNF).[10] The goal of developing therapeutically useful GSK-3β inhibitors is challenging, since the selectivity of a protein kinase inhibitor determines its effects and consequent adverse effects. Similar concerns impede progress on substances that modulate the BDNF/TrkB/CREB cascade.

Ideally, mood stabilizers should treat both mania and depression and prevent their recurrence. Treatment itself should not precipitate mania or depression or induce rapid cycling. The detailed molecular approach in development of newer mood stabilizers may not individually yield the improved efficacy that we seek, since modulation of a single molecular target is unlikely to provide the pharmacological "key" in the treatment of BD. Rather, BD should be viewed as a complex evolving disorder, where endogenous adaptive processes exacerbate the underlying pathology. Successful treatment of such an illness requires a multimodal approach – where intelligent polypharmacy should enhance patient care in therapy and prophylaxis.

TrkB – tyrosine kinase B receptor complex
CREB – cyclic adenosine monophosphate response element binding protein

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