# 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*

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