Lithium: the complex mechanisms of action of the simplest metal

Luchezar Hranov. Department of Psychiatry, Medical University of Sofia, Bulgaria.

Abstract

Lithium enhances neuronal resilience and hampers long-term neuronal (and by extension, mental) deterioration. Its "mood stabilising" properties are due to multi-level actions on the intracellular signal transduction pathways affecting the function of G proteins, of some intracellular messengers (mio-inositol, MARKS, Bcl-2, ER stress proteins, calmodulin-synapsin1-synaptotagmin complex), and of some key enzymes (adenilyl cyclase, protein kinases A, Cά and Cε, GSK-3, ERK, MAP-kinase). In the long run, mood-stabilising agents enhance blockade of excitotoxic/apoptotic pathways, phosphorylation and rearrangement of microtubular proteins, and regulation of the expression of genes implicated in processes involved in neuroplasticity, neuroprotection, even neurogenesis. Long-term "stabilisation of mood" has taught us the lesson that pharmacologic enhancement of neuroprotective/neurotrophic mechanisms carries a high promise for effective interventions not only in bipolar affective disorder and schizophrenia but in brain damage, dementias and other neurodegenerative diseases, and even in stress-induced mental disorders.

Key words: lithium, bipolar disorder, signal transduction, neuroplasticity.

Introduction

Lithium (Li+) is the lightest of the alkali metals, with a density only half that of water. It is used medically under the form of a cationic salt: lithium carbonate or citrate. As with many other drug therapies, the medicinal properties of lithium were discovered serendipitously and utilized long before its mechanisms of action could begin to be studied. Aretaeus of Cappadocia (AD 81 – 138) observed and documented cases of agitated insanity accompanied by mood elation and defined these states as "worsening of melancholia". He prescribed drinking water from certain alkaline springs containing lithium. The prescription was confirmed about 3 centuries later by his disciple Soranus of Efesus (1). In the 19th century, lithium salts were used therapeutically as part of popular tonics such as 7UP, as soporifics and as gout remedies.

Lithium was the first antimanic treatment discovered and it brought along the birth of the psychopharmacology revolution (4). The introduction of lithium salts for the treatment of bipolar affective disorder (BPD) by John Cade in 1949 revolutionised the pharmacotherapy of severe psychiatric illnesses. This landmark discovery not only relieved millions of suffering individuals but also changed the public and scientific perception of psychiatric disorders and triggered still ongoing attempts to define pathophysiological mechanisms for their origin and treatment (25).

Cade's work was followed up and validated by a series of European studies (39, 40). Over time, lithium became the gold standard for the management of the bipolar spectrum and the first of the so-called "mood stabilizers". A mood stabilizer is defined as a drug that benefits one or more primary mood states of BPD, is effective in the acute and maintenance phase of treatment, does not worsen any aspect of the disease (including enhancement of "switching"), and eventually reduces the number of illness episodes and prevents deterioration (16). By definition, such a stabilisation IS NOT ONLY control over acute full-blown/subsyndromal illness episodes but also dampening of mood lability, reducing disease progression, decreasing aggression and suicidality, improving functioning and enhancing cognition. Such complex effects could hardly be accomplished by a single pharmacological mechanism.

Exposure to lithium evokes a wide spectrum of behavioural, physiological, and developmental responses in diverse organisms. These effects have been explored in the hope of elucidating the

mechanisms of lithium therapeutic action (14). Lithium exerts multiple effects on numerous biological processes, such as embryonic development, haematopoiesis, glucose metabolism, heart function, and endocrine regulation (44). The therapeutic impact of lithium is much more complex than it may seem. Several other beneficial effects of lithium have been observed in psychiatry such as anti-aggressive effects in adults and children, symptomatic improvement of hyperactivity in schizophrenia, and behaviour benefits in mentally retarded patients. Moreover, lithium has been found to be useful in a broad range of neurological disorders (headaches, epilepsy, stroke, amyotrophic lateral sclerosis, fragile X syndrome, Huntington's chorea, Parkinson's disease and Alzheimer disease), endocrine disorders (hyperthyroidism, thyroid carcinoma, diabetes mellitus, inappropriate secretion of the antidiuretic hormone), haematological disorders (neutropenia, thrombocytopenia), dermatological disorders (seborrhoeic dermatitis), allergic disorders (asthma), and infectious diseases (AIDS-related dementia) (44).

Many drugs have been designed, by evolution or synthesis, to interact with a single specific protein receptor or enzyme. During the last 50 years, many biochemical actions of lithium have been identified, providing the basis for numerous hypotheses that were proposed to explain its mechanism of therapeutic action. Such an approach targeted to isolated sites of action makes it exceedingly difficult to integrate the often opposing actions of lithium at different sites into a single general biological mechanism. Recent research suggests that understanding how lithium works in the treatment of BPD requires a very different way of thinking about drug action. It now seems likely that multiple sites affected by lithium contribute to its mood-stabilizing action. Some of the numerous effects of lithium that have been identified may each provide a necessary, but individually insufficient, component of the therapeutic response. Thus, they should be conceptualised as being only facets of the very complex therapeutic effect of lithium (18).

Bipolar affective disorder (BPD)

BPD is a major health problem with potentially devastating consequences for affected individuals, their families and society. Recent studies have clearly shown that, although it has been regarded as a remitting disorder with a generally favourable long-term outcome, this may only represent the situation for a minority of patients. BPD is recognized by the World Health Organization as a leading debilitating neuropsychiatric disorder that affects about 1.3% of both sexes globally (34). The poor prognosis of these patients is illustrated by high rates of relapse, lingering residual symptoms, chronicity, cognitive and functional impairment, forensic complications, diminished quality of life and psychosocial disability. Patients with BPD I are prone to coexisting substance abuse, cardiovascular disease, diabetes mellitus, thyroid dysfunction, and have a 5¬ to 17-fold higher suicide rate than the general population. There is evidence that the illness is self-perpetuating and each episode increases the risk of future recurrence (2). In untreated patients, the disorder typically worsens owing to cycle acceleration; the frequency of episodes increases due to shortening of the length of symptom-free intervals. An increase in the number of episodes correlates with decreased cognitive abilities and deficits in social functioning.

Accompanying the observations about the poor clinical course and outcome for many patients, there has also been a growing appreciation that BPD is a disorder in which regional reductions in CNS volume, as well as reductions in the numbers and/or sizes of glia and neurons in discrete brain areas do really exist (2). It has been demonstrated that the neuronal density (especially of non-pyramidal GABAergic interneurons) in the dorso-lateral prefrontal cortex is decreased, the volume of the subgenual anterior cingular cortex is smaller than in healthy controls, and the third ventricle is often enlarged in BPD patients (10, 22, 26). The marked reduction in glial cell counts in the subgenual prefrontal cortex, orbital cortex, dorsal anterolateral prefrontal cortex, amygdala, basal ganglia, and dorsal raphe nuclei may contribute to impairments of neuronal structural plasticity by reducing the neuronal energy supply and by reduced glial-mediated clearing of excessive synaptic glutamate (15, 26, 31). Although the precise cellular mechanisms underlying these morphometric changes remain to be fully elucidated, the data suggest that BPD is associated with impairments of structural plasticity and cellular resilience (28, 31). It is not known whether these deficits constitute developmental abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to

other pathogenic processes, or are the sequelae of recurrent affective episodes per se. Structural damage is present before the first illness episode and progresses throughout the course of the disorder; that is why there is incomplete inter-episode recovery, many relapses and progressive pervasive functional deterioration (16). More recent evidence suggests that BPD affects intercellular signalling cascades, leading to impairments in structural and functional neural plasticity (32).

Accumulating evidence of the behavioural effects of lithium led to its approval by the FDA in 1970 for the treatment of mania in bipolar disorder; it still continues to be the mainstay of drug treatment. Its clinical applications include initial treatment of new manic episodes, long-term stabilisation of mood in BPD, and adjunctive therapy/prophylaxis in unipolar recurrent depression (13). Lithium has been proven to be effective in reducing both manic and depressive symptoms and in reducing the rate of suicide in bipolar patients (13).

The therapeutic action of lithium in BPD appears not to result from an effect at a single target site, but is rather an integrated complex of events which effectively adjusts neuronal activity at multiple levels (19). It is the integration of the multiple effects of lithium which is necessary to achieve the neurochemical balance and neuroanatomical stability facilitating the complex processes of mood recovery and stabilisation. Yet, it remains unclear how many of the multiple biochemical and molecular effects may explain the mechanism of the therapeutic benefit of lithium on BPD.

Mechanisms of action of lithium

With the passage of years it has been found that lithium induces multiple biochemical and molecular effects on neurotransmitter-receptor-mediated signalling, ion transport, signal transduction cascades, hormonal and circadian regulation, and gene expression (16). As neuroscience has developed over the past 50 years, the central paradigm for lithium action has shifted from monoamine metabolites via neurotransmitter receptors, second messengers, third messengers (transcription factors) to neuroprotection and neurogenesis, and in each of these lithium was found to have at least one major effect (8). Nevertheless, the precise underlying biochemical mechanisms of this drug are still not well understood and remain poorly defined (8, 12). Jope (19) has produced a summary of the manifold effects of lithium in the brain, as follows.

Lithium:

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

Importantly, rather than having unidirectional effects, lithium acts at multiple sites to adjust the balance between opposing influences (19). Moreover, an activity-dependent accumulation of lithium may be crucial for its therapeutic specificity and its ability to regulate synaptic function.

Neurotransmitter effects

Lithium was found to influence, to some extent, virtually every neurotransmitter. It reduces dopaminergic activity, enhances cholinergic and GABAergic neurotransmission, and blocks receptor supersensitivity in all major neurotransmitter systems (13). The levels of dynorphin, substance P, tachykinin, neuropeptide Y, and neurokinin A in certain brain regions are also increased following lithium treatment (19).

Accumulating evidence indicates that lithium has direct effects on glutamatergic neural transmission. Lithium stimulates glutamate release via activation of the N-methyl-D-aspartate (NMDA) receptors. Acute treatment increases synaptic concentrations of glutamate which, upon chronic lithium administration, leads to an increase in and stabilisation of glutamate uptake transporter capacity.

Several lines of evidence suggest that lithium alters neuronal excitability at hippocampal CA1 synapses, leading to enhanced excitatory postsynaptic potentials. This effect has been attributed to an increase in presynaptic excitability as well as to increases in synaptic efficiency. Alternatively, the effect of lithium on synaptic enhancement at CA1 synapses may arise from its ability to potentiate currents through the AMPA subtype of inotropic glutamate receptors by selectively increasing the probability of channel opening (38).

It is still not clear which, if any, neurotransmitter synthesis, uptake, and release processes contribute to the therapeutic action of lithium. It is possible that it is the adjusted balances (generally increased GABA/glutamate and acetylcholine/ catecholamine activity ratios), rather than actions on a single neurotransmitter, that facilitate mood recovery and stabilization (19).

Enzyme interactions

Several enzymes have been shown to be directly inhibited by lithium at therapeutically relevant concentrations. These include inositol monophosphatase (IMPase); inositol polyphosphate a-phosphatase; bisphosphate 3'-nucleotidase; fructose 1,6-bisphophatase; glycogen synthase kinase and phosphoglucomutase.
Lithium also affects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase. Plenge (33) proposed the theory that lithium inhibits enzymes which have essential cofactor cations, such as Na+, K+, Ca++, Mg++, and Zn++ by displacement of these cations from the enzyme molecule. Decrease of the hippocampal Na+-K+-ATPase activity (and thus, of Ca++ turnover) remains a viable contributory factor in the actions of lithium.

Signal transduction systems

Numerous studies have demonstrated that lithium increases basal levels of cyclic adenosine monophosphate (cAMP) but impairs receptor-coupled stimulation of cAMP production. Overall, it appears that these actions of lithium reduce the magnitude of fluctuations in cAMP levels by increasing the lowest basal levels and decreasing maximal stimulated increases, thus stabilising the activity of this signalling system (19). A primary action of cAMP is to stimulate the activity of cAMP-dependent protein kinase A (PKA). Lithium inhibits PKA-induced phosphorylation of cytoskeletal proteins which may contribute to long-term modulation of neuronal structure and function.
The major adverse effects of lithium therapy - hypothyroidism and nephrogenic diabetes insipidus - have been postulated to arise from the effects lithium has on thyroid-stimulating-hormone-sensitive adenylate cyclase, and on antidiuretic hormone (vasopressin)-sensitive adenylate cyclase, respectively (41).

Lithium is a potent inhibitor of inositol monophosphatase, the enzyme that converts inositol monophosphates to free inositol (43). Reduced inositol levels following lithium administration are most conspicuous in the hypothalamus and the astrocytes (19). The "inositol depletion 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 (3). The primary second messengers produced by the phosphoinositide signal transduction system are inositol trisphosphate (IP3), and diacylglycerol (DAG). The IP3 arm of the system releases intracellular calcium from internal stores which then activates calcium and/or calmodulin-dependent protein kinases. The DAG arm of the system produces activation of protein kinase C (PKC) which has various critical substrates.
The PKC family of 12 isozymes regulates glucose transport, ion conductance, neural excitability, neurotransmitter release, gene expression, dendrite spine morphology and plasticity (11). PKC isoforms differ in structure, subcellular localization, tissue specificity, mode of activation, and substrate specificity (36). They are translocated from cytosol to membrane upon activation by DAG and phosphorylate NMDA and AMPA receptors.

The PKC inhibitor tamoxifen has demonstrated a robust anti-manic efficacy (11, 48, 49). Chronic application of lithium reduces specifically the levels of isotypes PKCα and PKCε (24). PKC activity

increases in the prefrontal cortex following stress or stimulant use and is decreased by chronic treatment with lithium. Excessive activation of PKC dramatically impairs cognition in mammals. Six-week treatment with lithium abolishes this effect.

Long-term treatment with lithium reduces significantly the levels of one of the major substrates of PKC, MARCKS (myristoylated alanine-rich C kinase substrate). MARCKS plays a key role in transducing extracellular signals to alterations in the conformation of the actin cytoskeleton which is crucial to morphogenesis and secretion. Its down-regulation following chronic lithium administration may alter membrane structure and stabilise aberrant neuronal activity in different brain areas (24).

Lithium activates the intracellular activated protein kinase/extracellular signal-related kinase (MAPK/ERK) signalling pathway which is used by neurotrophins, neurotransmitters, and neuropeptides to exert their neurotrophic and neuroprotective effects through specifically enhancing progenitor cell proliferation and differentiation, neuronal process growth and regeneration, neuronal survival, and long-term synaptic remodelling and plasticity (17). The final result is phosphorylation and activation of the transcription factor CREB (cAMP response element binding). CREB regulates the expression of many different genes, including B-cell lymphoma 2 (bcl-2) and brain-derived neurotrophic factor (BDNF) to enhance neuroprotection and neuronal survival mechanisms (27).

Lithium may modulate the production of nitric oxide and, in addition, may inhibit phospholipase A2, an enzyme that mediates the production of arachidonate which, in turn, leads to reduced activation of PKC, alterations in cell growth and apoptosis (pre-programmed cell death), and changes in the production of eicosanoids. Thus, lithium may affect central inflammatory processes and exert immunostimulant and antimicrobial activity (42).

Mitochondrial function

Mitochondria play a critical role in regulating energy production via oxidative phosphorylation and regulation of intracellular calcium, and are also critical mediators of cellular apoptosis (36). Increasing evidence suggests that they may also be integrally involved in general processes of synaptic plasticity (35).

Many lines of evidence link BPD to a fundamental abnormality in oxidative energy generation. Both brain and somatic energy generation are altered, and high rates of deletions in mitochondrial DNA are seen, as well as a reduction in the activity of complex 1 of the mitochondrial chain. Increased lipid peroxidation, a consequence of uncompensated oxidative stress, is consistently documented in BPD. Oxidative damage results in damage to membrane phospholipids, leading to alteration in fluidity and aggregation of oxidised protein, which may result in impairment of mood-stabilising neurones, and can ultimately lead to neuronal cell death by apoptosis (2). Chronic lithium treatment reduces oxidative stress.

Altered calcium dynamics is the most reproducible biological measure in the pathophysiology of BPD. A large movement of calcium into the mitochondria will exceed the mitochondrial capacity to export protons, potentially interrupting adenosine triphosphate synthesis and the activation of the permeability transition pore with release of cytochrome C, thus initiating cellular apoptosis. In addition, excessive production of reactive oxygen species (or free radicals) triggered by mitochondrial dysfunction may lead to oxidative stress, regardless of whether or not this is related to lower antioxidant capacity. Lithium affects beneficially key enzymes on the mitochondrial membrane via its neuroprotective actions, described below (35).

Transcription factors and gene expression

Many of the genes putatively involved in the pathogenesis of BPD are regulating 1) cellular signalling; 2) critical cytoskeletal proteins; 3) trophic effects and cell survival; 4) metabolic events and cell death (29). The underlying deviant brain growth, organization and ageing, resulting from their dysfunction, are likely to determine the lifetime course of psychopathology (9).

Transcription factors fulfil the critical functions of transmitting and regulating signals to the nucleus, allowing cells to respond to a changing environment through alterations in gene expression. They may be selectively influenced by lithium both as a result of modulation of the activities of specific signalling systems and as being specific targets for lithium (19). Lithium modulates the activity of several transcription factors (AP1, CREB, NF-κB) and increases mRNA levels for c-fos genes and for nitric oxide synthase 2, thus modulating gene expression. The net effect is an overall stabilisation and minimisation in the magnitude of signal fluctuations at the level of gene expression (19).

Neuroplasticity, neuroprotection and cytoskeletal remodelling

"Neuroplasticity" subsumes diverse processes of vital importance by which the brain perceives, adapts to, and responds to a variety of internal and external stimuli (49). Loosely defined, neurotrophic effects augment proliferation, differentiation, growth, and regeneration of neurons while neuroprotective effects slow or halt the progression of neuronal atrophy or cell death following the onset of insult, disease, or clinical decline (8, 17).

Lithium may enhance cellular resilience and plasticity in dysfunctional synapses and neuronal circuitry implicated in psychiatric disorders (17). The neurotrophins are a family of regulatory factors. They are known to mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity. Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by activating the extracellular-regulated kinase (ERK) signalling pathway (36). Lithium increases mRNA and protein levels of neurotrophins such as BDNF, glial cell-line derived neurotrophic factor (GDNF), neurotrophin 3 (NT-3), and vascular endothelial growth factor (VEGF) in cultured cells and brain regions. Nevertheless, the majority of the neuroprotective and neurotrophic effects of lithium appear to occur through its influences on two key proteins in the brain, bcl-2 and GSK-3β.

The bcl-2 (B-cell lymphoma/leu¬kaemia-2) family includes both pro- apoptotic and anti-apoptotic proteins embedded in the inner mitochondrial membrane, although they may also be present in nuclear membranes and in the endoplasmic reticulum (26). The expression and/or activation of pro-apoptotic bcl-2 family members (e.g. bad and bax) may increase mitochondrial membrane permeability, while anti-apoptotic members (e.g. bcl-2 and bcl-xl) have the opposite effect (26). 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. Bcl-2 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 (42).

The transcription factor PEBP2P (polyoma enhancer binding protein 2P) is one of the genes identified thus far to have markedly increased expression and functioning following lithium treatment. The end result is a dramatic increase in the levels of the neuroprotective protein bcl-2. Such increases have been registered predominantly in the frontal cortex (particularly in layers II and III), the hippocampus and the striatum (6). Interestingly, lithium also increases the expression of bcl-2-associated athanogene (bag-1), which is known to attenuate glucocorticoid receptor nuclear translocation, to activate the ERK/MAP kinases, and to potentiate the anti-apoptotic functions of bcl-2 (50).

Lithium exerts a direct inhibitory effect on glycogen synthase kinase (GSK-3), a multifunctional and highly active serine/threonine kinase that regulates diverse signalling pathways (e.g., the phosphoinositide 3-kinase pathway, the Wnt pathway, PKA, and PKC), and the ensuing neuronal cytoskeletal rearrangements may be a significant consequence of lithium administration. In general, increased activity of GSK-3 is pro-apoptotic, whereas inhibiting GSK-3 prevents apoptosis. In mammals, two closely related isoforms - GSK-3α and GSK-3β - are present. The GSK-3β isoform is highly expressed in neural tissue where its expression is regulated during development. GSK-3 isoforms are important regulators of glycogen synthesis, gene transcription, axonal remodelling in developing neurons, cytoskeletal modelling and organization, growth of neural tissue, synaptic and neuronal plasticity, cellular structure and resilience, and apoptotic processes (20, 21). Its downstream

targets include transcription factors like c-Jun, proteins bound to microtubules (Tau, microtubule-associated protein 1B, kinesin light chain), cell cycle mediators (cyclin D), and metabolic regulators (glycogen synthetase, pyruvate dehydrogenase) (36). Following exposure to stressful conditions GSK-3 can have multiple effects that could impair neural plasticity and in potentially lethal conditions could facilitate the apoptotic process. These include actions of GSK-3 that both contribute to apoptosis and actions that block anti-apoptotic processes (21).
The inhibition of GSK-3β by lithium can induce significant changes in microtubule assembly resulting in significant neuroplastic changes in discrete brain regions and alterations in interneuronal connectivity. In fact, GSK-3 inhibition directly influences gene transcription, leading to anti-apoptotic effects and improved cell structural stability (7).

GSK-3 also directly regulates the dopaminergic, glutamatergic, and serotonergic neurotransmitter systems. It has been suggested that GSK-3 regulates behaviour by affecting β-catenin, glutamate receptors, circadian rhythms, and neurotransmission (23). All of these have been implicated in the pathophysiology of severe mood disorders, and all of them are affected by lithium treatment.

Neurotrophic effects

N-acetyl aspartate (NAA) is an amino acid localised exclusively in mature neurons. It 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. Chronic lithium treatment increases levels of NAA in rodent brain, human neuronal cells in culture, as well as in vivo in human bipolar patients and healthy volunteers. The lithium-induced increases in NAA seem to occur mainly in the frontal and temporal lobes. Interestingly, there is no correlation between the increase in NAA and the lithium levels (42).

Chronic behavioural stress shortens apical dendrites in the CA3 region of the hippocampus in rodents. Lithium treatment initiated 2 weeks before the stress and continued throughout a 3-week period of stress attenuated these stress-induced reductions in apical dendritic lengths (45).

Several additional reports and meta-analyses have documented increased total hippocampal volume in patients treated with lithium compared with unmedicated patients (47). Pooled imaging data showed cerebral volume reductions in BPD that were significantly associated with illness duration. Bipolar patients who were not on lithium therapy showed significant decrease in cerebral and hippocampal volumes, whereas patients treated with lithium showed significantly increased hippocampal and amygdala volumes (15). Recent studies using high-resolution magnetic resonance imaging have convincingly shown that the amygdala volume is smaller in unmedicated bipolar patients and larger in patients with BPD on mood-stabiliser treatment (37).

Prominent volumetric abnormalities of the anterior cingulate cortex have been reported in BPD, and chronic treatment with lithium has been associated with increased grey matter volumes in this region (30).

Hence, the existing data point to neurotrophic and neuroprotective actions of lithium in multiple areas of the limbic and/or prefrontal network by increasing cellular resiliency, enhancing synaptic plasticity and modulating neuronal morphology.

Inhibition of GSK-3β contributes to lithium-induced neural cell proliferation (34). An in vivo study showed that lithium increased survival of newborn cells in the hippocampus (5, 46). These results suggest that chronic lithium treatment may not only exert robust neuroprotective effects (as has been demonstrated in a variety of preclinical paradigms) but may also have neurotrophic effects in humans.

Conclusions

Despite intensive research, the crucial question of how lithium is able to alter mind and mood remains a mystery (44). It is also unclear how the action of lithium on ubiquitously expressed molecules that

are mostly involved in the regulation of cell signalling and not on specific neurotransmitter systems can explain its relative selectivity as a therapeutic agent in psychiatry (12).

It has become evident that the research strategy of trying to find one molecular target of lithium therapeutic efficacy does not provide any satisfactory explanation (44). Rather than looking for a single site of action, many actions of lithium must, and can, be integrated to obtain a cohesive picture of how neuronal function is modulated by long-term exposure to lithium. Simultaneous multiple actions of lithium (some of which are bimodal), must be considered to be critical for the therapeutic response. These complex effects support neural plasticity and stabilise neurotransmitter balances, signalling activities, and gene expression, each of which may make a necessary, but individually insufficient, contribution to the therapeutic effects of lithium. The critical property of lithium appears to be that it is able to act at multiple sites to adjust the balance, and dampen the magnitudes of fluctuations, of positive and negative inputs to neuronal function. This allows lithium to normalise the complex components of mood disorders and to have multiple therapeutic effects (19).

Lithium alters intracellular and intercellular signalling in critical brain regions in a unique way. New insights of the diverse and complex actions of lithium open up an entirely new field of research. They carry profound implications in the neurobiology of bipolar disorder, implicating the inflammatory response, neuronal atrophy and death (41). Moreover, they throw light on new therapeutic approaches to presently untreatable neurodegenerative diseases (16).

GP Comment

What have I learned from this paper?

This fascinating article described the multiple biochemical and molecular effects of this medicinal metal which has huge therapeutic potential in 'mood-stabilisation' and was first used by Aretaeus of Cappadocia (AD 81-139)!

Bipolar disorder affects 1.3% of both sexes globally and is a debilitating neuropsychiatric disorder. Each episode increases the risk of a future recurrence and results in decreased cognitive ability and social functioning.

The exact mode of action of lithium is unclear. Rather than an effect at a single target site, lithium causes an integrated complex of events which adjusts neuronal activity at multiple levels to achieve the neurochemical balance and neuroanatomical stability. It enhances neuronal resilience and dampens neuronal fluctuation and deterioration.

The effect of lithium on long-term stabilisation of mood has huge therapeutic potential in not only bipolar disorder and schizophrenia but also in all mood disorders and stress-induced mental illness. In addition the neurotrophic and neuroprotective effects, chronic lithium therapy offers promising prospects for patients with brain damage, dementia and other neurodegenerative disorders.

This article emphasised to me how much we have yet to learn about the mind, mood, the interaction between mental and physical health and the aetiology and treatment of ill-health.

Dr Anthea Robinson, GP, Bedfordshire.

References

1. Angst J, Marneros A. Bipolarity from ancient to modern times: conception, birth and rebirth. J Affect Disord. 2001;67:3-19.
2. Berk M, Conus P, Kapczinski F, Andreazza AC, Yucel M, Wood SJ, et al. From neuroprogression to neuroprotection: implications for clinical care. MJA. 2010;193:36-40.
3. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. Cell. 1989;59:411-9.
4. Cade JF. Lithium salts in the treatment of psychotic excitement. Med J Aust. 1949;2:349-52.
5. Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. J Neurochemistry. 2000;75 (4):1729 – 34.
6. Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, Manji HK. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. J Neurochem. 1999;72:879-82.
7. Chin PC, Majdzadeh N, D'Mello SR. Inhibition of GSK3beta is a common event in neuroprotection by different survival factors. Brain Res Mol Brain Res. 2005;137:193-201.
8. Chiu CT, Chuang DM. Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. Pharmacol Ther. 2010;128 (2):281 – 304.
9. DeLisi L. Critical overview of current approaches to genetic mechanisms in schizophrenia research. Brain Res Rev. 2000;31:187-92.
10. Drevets WC, Price JL, Simpson JR. Subgenual prefrontal cortex abnormalities in mood disorders [letter]. Nature. 1997;386:824-7.
11. Einat H, Yuan P, Szabo ST, Dogra S, Manji HK. Protein kinase C inhibition by tamoxifen antagonizes manic-like behavior in rats: implications for the development of novel therapeutics for bipolar disorder. Neuropsychobiology. 2007;55:123-31.
12. Freland L, Beaulieu JM. Inhibition of GSK3 by lithium, from single molecules to signaling networks [Art. 14]. Front Mol Neurosci. 2012;1-7.
13. Goodwin FK, Baldessarini RJ, Dunner DL. The use of lithium in treating bipolar disorder. CNS Spectrums. 2002;7 (11):TM1-TM12
14. Gurvich N, Klein PS. Lithium and valproic acid: parallels and contrasts in diverse signaling contexts. Pharmacol Therapeutics. 2002;96:45-66.
15. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 2011;69:326-35.
16. Hranov LG. Do neurons have mood and how can it be stabilized? [abstract]. Psychiatria Danubina. 2009;21 Suppl 2:S158.
17. Hunsberger J, Austin DR, Henter JD, Chen G. The neurotrophic and neuroprotective effects of psychotropic agents. Dialogues Clin Neurosci. 2009;11:333-48.
18. Jope RS. A bimodal model of the mechanism of action of lithium. Molecular Psychiatry. 1999;4: 21-5.
19. Jope RS. Anti-bipolar therapy: mechanism of action of lithium. Molecular Psychiatry. 1999;4:117-28.
20. Jope RS. Lithium and GSK-3: one inhibitor, two inhibitory actions, multiple outcomes. Trends Pharmacol Sci. 2003;24:441-43.
21. Jope RS, Roh MS. Glycogen synthase kinase-3 (GSK3) in psychiatric diseases and therapeutic interventions. Curr Drug Targets. 2006;7 (11):1421-34.
22. Lim KO, Rosenbloom MJ, Faustman WO, Sullivan EV. Cortical gray matter deficit in patients with bipolar disorder. Schizophr Res. 1999;40:219-27.
23. Machado-Vieira R, Salvadore G, DiazGranados N, Ibrahim L, Latov D, Wheeler-Castillo C, et al. New therapeutic targets for mood disorders. Scientific World Journal. 2010;10:713-26.
24. Manji HK, Lenox RH. Signaling: cellular Insights into the pathophysiology of bipolar disorder. Biol Psychiatry. 2000;48:518-30.
25. Manji HK, McNamara R, Chen G, Lenox RH. Signalling pathways in the brain: cellular transduction of mood stabilisation in the treatment of manic-depressive illness. Aust N Z J Psychiatry. 1999;33 Suppl: 65-83.
26. 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;48:740-54.
27. Manji HK, Moore GJ, Chen G. Bipolar disorder: leads from the molecular and cellular mechanisms of action of mood stabilisers. BJP. 2001;178:107-19.
28. Manji HK, Young LT. Structural plasticity and neuronal resilience: are these targets for mood stabilizers and antidepressants in the treatment of bipolar disorder? Bipolar Disord. 2002;4 (2):77-9.
29. Manji HK, Zhou R, Chen G. Neuroplasticity and cellular resilience in bipolar disorder. Bipolar Disord. 2002:4 Suppl 1:56-7.
30. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK, Manji HK. Lithium-induced increase in human brain grey matter. Lancet. 2000;356:1241-2.
31. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci USA. 1998;95:13290-5.
32. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: convergence of mechanisms. Neuropsychopharmacology. 2008;33:88-109.
33. Plenge P. Lithium effects on brain energy metabolism. In: Gabay SJ, Harris BT, editors. Metal ions in neurology and psychiatry. New York: Alan R. Liss, Inc.; 1985. p. 153-64.
34. Qu Z, Sun D, Young W. Lithium promotes neural precursor cell proliferation: evidence for the involvement of the non-canonical GSK-3P-NF-AT signaling. Cell Biosci. 2011;1:18.
35. Quiroz JA, Gray NA, Kato T, Manji HK. Mitochondrially mediated plasticity in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology 2008;33:2551-65.
36. Quiroz JA, Machado-Vieira R, Zarate CA Jr, Manji HK. Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. Neuropsychobiology. 2010;62:50-60.
37. Savitz J, Nugent AC, Bogers W, Liu A, Sills R, Luckenbaugh DA, et al. Amygdala volume in depressed patients with bipolar disorder assessed using high resolution 3T MRI: the impact of medication. Neuroimage. 2010;49 (4):2966-76.
38. Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. Trends in Neurosciences. 2012;35 (1):36-46.
39. Schou M. Biology and pharmacology of lithium ion. Pharmacol Rev. 1957;17-58.
40. Schou M, Juel-Nielsen N, Stromgren E, Voldby H. The treatment of manic psychoses by the administration of lithium salts. J Neurol Neurosurg Psychiatry. 1954;17:250-60.
41. Segal J. Lithium - an update on the mechanisms of action: pharmacology and signal transduction. S Afr Psychiatry Rev. 2004;7 (Pt 1):4-11.
42. Segal J. Lithium - an update on the mechanisms of action: neural effects and neuroanatomical substrate. S Afr Psychiatry Rev. 2004;7 (Pt 2):18-24.
43. Sherman WR, Gish BG, Honchar MP, Munsell LY. Effects of lithium on phosphoinositide metabolism in vivo. Fed Proc. 1986;45:2639-46.
44. Strunecka A, Patocka J, Sarek M. How does lithium mediate its therapeutic effects? J Appl Biomed. 2005;3:25-35.
45. Wood GE, Young LT, Reagan LP, Chen B, McEwen BS. Stress-induced structural remodeling in hippocampus: prevention by lithium treatment. Proc Natl Acad Sci USA. 2004;101:3973-8.
46. Yan XB, Hou HL, Wu LM, Liu J, Zhou JN. Lithium regulates hippocampal neurogenesis by ERK pathway and facilitates recovery of spatial learning and memory in rats after transient global cerebral ischemia. Neuropharmacology. 2007;53:487-95.
47. Yucel K, Taylor VH, McKinnon MC, McDonald K, Alda M, Young LT, et al. Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment, Neuropsychopharmacology. 2008;33:361-7.
48. Zarate CA, Manji HK. Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder. CNS Drugs. 2009;23:569-82.
49. Zarate CA Jr, Singh J, Manji HK. Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. Biol Psychiatry. 2006;59:1006-20.
50. Zhou R, Gray NA, Yuan P, Li X, Chen J, Chen G, et al. The anti-apoptotic, glucocorticoid receptor cochaperone protein BAG-1 is a long-term target for the actions of mood stabilizers. J Neurosci. 2005;25:4493-502.