1.1 Introduction

Lithium, from the Greek word ‘lithos’ or stone, is the smallest and lightest solid element – a monovalent cation appearing third on the periodic table. It is well known for its use in batteries, metal alloys, glass manufacture and for its clinical use in the treatment of manic depression or bipolar disorder (BD), a chronic disorder which affects between 1 and 2% of the population and is characterized by episodic periods of elevated and/or depressed mood. This disorder severely reduces patients’ quality of life and dramatically increases the likelihood of these patients committing suicide. Lithium’s clinical role has given rise to extensive amounts of scientific research; however, despite this, there is still considerable debate regarding its medicinal targets. It is also unclear how such a structurally simple ion can have such a profound effect on specific and complex medical disorders such as BD.

For many years lithium’s structural simplicity may have discouraged the development and patenting of alternative anti-manic agents – how can one modify and patent a monovalent ion? The fact that it has largely been ignored by pharmaceutical companies can give the impression that it is an ‘old drug’, with little new therapeutic potential. However, in truth, it is still highly successful in the treatment for BD. In addition, it is now increasingly being used as a tool by developmental and cell biologists, and also shows great promise in the treatment of other medical disorders.
In this chapter we will introduce lithium and its medicinal history, describe its biological actions, its known targets in biological systems and its therapeutic applications.

1.2 The Inorganic Chemistry of Lithium

Lithium is a member of group 1 (1A) alkali metals, has an atomic number of 3, an atomic weight of 6.941 and contains a single valence electron. In its pure form it is a soft silvery white metal, turning grey on exposure to air. Because of its reactivity in the metallic state, it is only found in nature as an ore or at low concentrations as a soluble salt, e.g. it is present in river waters at \( \sim 0.002 \text{ mg/l} \). But it has also been found at higher levels in naturally occurring springs which have previously been associated with health improvements (e.g. Lithia Springs Mineral Water, Georgia, USA).

The most important commercial ore containing lithium is spodumene, \( \text{LiAl(SiO}_3\text{)}_2 \). The extraction of lithium from this ore occurs by converting it to the soluble chloride salt. This process starts by heating spodumene to around \( 1100 \degree \text{C} \). This is then mixed with sulphuric acid and water to form lithium sulphate (\( \text{Li}_2\text{SO}_4 \)). This is washed with sodium carbonate (\( \text{Na}_2\text{CO}_3 \)) to form a precipitate of the lithium carbonate (\( \text{Li}_2\text{CO}_3 \)) (Equation 1.1). Reaction of lithium carbonate with hydrochloric acid gives rise to lithium chloride (Equation 1.2).

\[
\text{Li}_2\text{SO}_4 + \text{Na}_2\text{CO}_3 \rightarrow \text{Na}_2\text{SO}_4 + \text{Li}_2\text{CO}_3 \\
\text{Li}_2\text{CO}_3 + 2\text{HCl} \rightarrow 2\text{LiCl} + \text{CO}_2 + \text{H}_2\text{O}
\]

(1.1)  

(1.2)

As a salt, lithium has the smallest ionic radius, the largest field density at its surface and is the least reactive of the alkali metals. The very small diameter of the lithium ion in relation to water means that molecular packing gives it an anomalously large hydration shell in proportion to other group 1 elements. Thus in experiments examining the effect of lithium salts on osmolarity, the corresponding sodium salt is often used as a control, as this provides the closest approximation to lithium’s hydration shell size.

Although the hydration shell of lithium is similar in size to sodium, its ionic radius is much closer to that of the magnesium ion (Table 1.1). This similarity allows lithium ions to compete with magnesium ions for binding sites in proteins.\(^3\)–\(^5\) As magnesium ions interact with hundreds of proteins, this suggests that lithium may inhibit numerous enzymes. However, the relative specificity of the lithium effect suggests that only proteins with very low affinities for magnesium are targeted by therapeutic concentrations of the drug. The total magnesium concentration of the cell is between 10 and 15 mM, but the free concentration of magnesium is between 0.5 and 1.0 mM. This is the same concentration of lithium found in plasma from patients undergoing lithium therapy.\(^6\)
1.3 Biology of Lithium

1.3.1 The history of lithium therapeutics

Garrod described the medical use of lithium in 1859 for the treatment of rheumatic conditions and gout – and in particular ‘brain gout’. The hypothesis behind the use of lithium at this point was based on its ability to dissolve nitrogen-containing compounds, called urates or uric acid, which were thought to build up in the body giving rise to many illnesses. This is certainly true for gout, but the idea was extended to include many other human physical disorders. By the 1880s, Carl Lange and others\(^7\) were using lithium for the treatment of BD, and lithium carbonate and citrate were described in the British Pharmacopoeia of 1885.

In addition to the treatment of patients, the urea hypothesis spurred the development of the lithium tonic and its increasing use in common food stuffs. The most notable today is 7 UP, originally introduced in 1929 as ‘Bib-Label Lithiated Lemon-Lime Soda’. The lithium was removed in 1950. The decline of the urea hypothesis and the lack of a credible therapeutic mechanism for lithium lead to its disuse as a therapeutic agent until it was re-discovered in 1949 by John Cade.\(^8\) He was continuing the search for a toxin which may cause BD, and was working on the premise that these toxins may be excreted in the urine of BD patients. He thus injected concentrated urine samples from these patients and control subjects into the abdomen of Guinea pigs, and found that bipolar patient urine had greater toxicity than that of the control subject. To identify what this toxic compound was, he then tested different forms of nitrogen-containing compounds found in urine, and identified urea as being the most toxic. His line of reasoning continued, that dissolving this urea may alleviate the toxicity, so he tried co-injecting urea with alkali metals, only to find that lithium causes sedation and stupor in the animals. This suggested that lithium may have sedative or mood-control properties. Following testing of lithium toxicity on himself, he then administered it to BD, depressed and

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Lithium</th>
<th>Beryllium</th>
<th>Boron</th>
<th>Sodium</th>
<th>Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Atomic no.</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>4 coordinate</td>
<td>73</td>
<td>41</td>
<td>25</td>
<td>113</td>
<td>71</td>
</tr>
<tr>
<td>6 coordinate</td>
<td>90</td>
<td>59</td>
<td>41</td>
<td>116</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 1.1 The chemical symbol, atomic charge and atomic number of lithium and its neighbouring elements on the periodic and their ionic radii table in different coordination states. Units are given in pico moles.
schizophrenic patients, and found huge improvements in the BD patient group. As no effective drug treatments existed at the time for any major psychiatric disease, this was an extremely exciting event and effectively places lithium as the first modern psychopharmacological agent.

Cade’s work, however, rapidly became overshadowed by two events. First, on the same year as Cade’s discovery, the Food and Drug Administration (FDA) banned lithium following the death of four US patients due to lithium overdose. It was thought at the time that lithium chloride could be used to reduce sodium chloride intake, and would therefore be useful in the treatment of hypertension. Doses of up to 14 g per day were used in these cases, which were extremely high compared with modern lithium use. The second event to overshadow Cade’s re-discovery of lithium was the discovery of chlorpromazine, the first antipsychotic. This molecule heralded a new era in the development of psychotropic drugs for the treatment of schizophrenia and major depression.

Fortunately, throughout the 1950s Schou and others continued to investigate the use of lithium and demonstrated that it could be used safely in the treatment of BD. It was re-approved by the FDA in 1972 and is now prescribed in over 50% of BD cases, although it is very common that it is used in combination with other drugs. It is marketed under a variety of names including Lithicarb®, Quilonum SR®, Lithotabs® and Librium®. It has also clearly been shown to reduce the risk of suicide in mood disorder patients, and it has considerable socioeconomic impact, e.g. it has been estimated that it has saved around $8 billion in the US alone in 1991.

1.3.2 Lithium and the body

Lithium therapy is always taken orally, usually as lithium carbonate as this causes least irritation to the stomach, to a total dose of up to 30 mmol (≤2 g) per day. Treatment is monitored by blood concentration 12 h after administration. The therapeutic index for lithium, which represents the concentration window from efficacy to toxicity, is very narrow, occurring between 0.4 and 0.8 mM. Interestingly, lithium treatment alters magnesium balance, and concentrations of magnesium ions are altered in both the blood and the urine following lithium treatment. This is consistent with displacement of magnesium by lithium from cellular binding sites.

In general, lithium distributes uniformly among the body tissues, and most cells of the body experience an external lithium concentration of less than 2 mM, even at the highest clinical doses. However, local accumulation occurs in some tissues, but not those of the brain. In particular, lithium accumulates to a moderate degree in endocrine glands and to a high concentration at the tip of the papilla in the kidney. At a blood concentration of 1 mM, the renal papillary can reach 60–65 mM.

Lithium is not soluble in lipids and hence will not cross the plasma membrane. There are a number of routes for lithium entry into the cell – the most
prevalent being lithium–sodium counter-transport,\textsuperscript{13} anion exchange\textsuperscript{14} and through other unrelated transport molecules. It is also not bound to proteins in plasma or tissue, unlike other BD treatments.

In addition to its therapeutic uses, embryologists have long known lithium to be a teratogen – a drug that affects patterning and proportion of cell types in the developing embryo. For example, in sea urchins, lithium causes vegetalization of the animal blastomeres,\textsuperscript{15} and in vertebrates such as *Xenopus*\textsuperscript{16} and zebrafish\textsuperscript{17} it causes expansion of the dorsal mesoderm and duplication of the dorsal axis. These effects are not restricted to animals, as lithium treatment of *Dictyostelium*, a non-metazoan eukaryote, leads to mis-specification of spore and basal disc cell fate.\textsuperscript{18} It was therefore assumed that lithium treatment will be teratogenic in humans, as seen for the other mood stabilizers valproic acid (VPA) and carbamazepine (CBZ).\textsuperscript{19} However, despite the assumed clinical risk, there are surprisingly few reports of teratogenic effects of lithium on human development, although some reports have suggested an increased risk of congenital heart defects.\textsuperscript{19} The difference in these teratogenic rates may reflect dosage, as embryological experiments carried out in the laboratory generally use higher than therapeutic lithium concentrations.

### 1.4 Targets of Lithium

It is well accepted that there are two general targets of lithium in the cell – the enzymes glycogen synthase kinase-3 (GSK-3) and the phosphomonoesterase family (PMEs).\textsuperscript{20} No other direct targets of lithium have been found over the last 30 years, despite considerable amounts of research, although many other targets have been suggested. These include inhibiting adenyl cyclase\textsuperscript{21} and G proteins,\textsuperscript{22} and interacting with cell surface receptors to affect guanidine trisphosphate (GTP) binding.\textsuperscript{23} These lithium targets are more likely to be affected indirectly through altered GSK-3 or PMEs’ activities, or were found to be lithium targets at artificially high lithium concentrations that do not occur in the body during lithium therapy.

#### 1.4.1 Glycogen synthase kinase-3

Lithium inhibits GSK-3 kinases, a family of highly conserved serine/threonine protein kinases that have been identified in all eukaryotes examined to date. In vertebrates, GSK-3 is found as two isoforms: GSK-3\textsubscript{α} and GSK-3\textsubscript{β}. Lithium has been demonstrated to inhibit both these isoforms \textit{in vitro} and \textit{in vivo} through competition for magnesium ion binding (see section 1.2).\textsuperscript{24,25} GSK-3 phosphorylates its amino acid target at an unusual substrate recognition site which contains phosphorylated serine or threonine four residues towards the
C’ terminus of the phospho-donor site (Figure 1.1). This acts as a docking site to anchor GSK-3 on its substrate. The resulting phosphorylation can then be used to prime further neighbouring residues. Loss of this priming phosphorylation decreases affinity with the substrate by 100–1000-fold.26 This also means that in most cases GSK-3 works in concert with other kinases.

Glycogen synthase kinase-3 was first identified as an enzyme that phosphorylates and inactivates glycogen synthase27 in the insulin response pathway (Figure 1.2). In this pathway, insulin turns on GSK-3 activity to inhibit glycogen synthesis. Consequently, in diabetic rat hepatocytes, lithium restores glycogen synthesis in the presence of an overactive insulin pathway. However, GSK-3 has many other targets within the cell including a number of important transcription factors and cytoskeletal proteins.

A significant GSK-3 substrate is the protein β-catenin, which regulates gene expression by binding to the LEF-1/TCF-3 family of transcription factors.28 GSK-3 phosphorylation of β-catenin leads to its degradation and hence prevents its accumulation in the nucleus where it binds T-cell factor transcription factors (TCFs) (Figure 1.2). This phosphorylation event is regulated by binding to axin, which brings GSK-3 and a priming kinase, casein kinase 1 (CK 1), in contact with β-catenin.29 Formation of the axin complex is regulated by the binding of the extra-cellular glycoprotein Wnt to its cell surface receptor Frizzled. In this way Wnt signalling can regulate gene expression through control of β-catenin degradation. The number of cellular events found to be regulated by Wnt signalling is increasing and includes the control of cell fate during development and cell proliferation. Loss of the GSK-3 phosphorylation sites from β-catenin, deletions of adenomatous polyposis coli protein (APC), another component of the axin–β-catenin protein complex, and mutations of axin itself are all associated with various forms of human cancer.30 β-Catenin is also a component of adherens junctions which anchor the actin cytoskeleton to points of cell–cell contact via cadherin proteins on the cell surface. GSK-3-mediated changes in β-catenin stability do not affect adherens
junction-mediated cell contact, and cell contact does not alter regulation of \(\beta\)-catenin-mediated gene expression.

In addition to its role in cell signalling, GSK-3 is also involved in the regulation of the cell cytoskeleton. Inhibition of GSK-3 by lithium, or other GSK-3 inhibitors, affects both microtubule dynamics\(^{31}\) and microtubule polarity.\(^{32}\) These effects are clearly seen in neurons which rely heavily on the microtubule cytoskeleton to grow and maintain their morphology. Lithium treatment causes changes in axonal branching and behaviour of the developing growth cone and thus, the structure of the synapse. Inhibition of GSK-3 in dividing cells also leads to misalignment of the mitotic spindle, affecting chromosome segregation\(^{33}\) and the plane of cell division during development.\(^{34}\) GSK-3 substrates involved in these structural changes include microtubule-associated protein 1B (MAP1B), Tau and APC. Both MAP1B and Tau are microtubule-binding proteins that regulate microtubule dynamics. Tau is hyper-phosphorylated by GSK-3, leading to the generation of the paired helical

Figure 1.2  Glycogen synthase kinase-3 functions in a variety of signalling pathways. Wnt signalling via Frizzled (Frz) and Dishevelled (Dsh) functions to inhibit GSK-3 activity. This effects the phosphorylation and thus stability of the cell cytoskeleton via cell structural components such as microtubule-associated protein MAP 1B and Tau, and the degradation of \(\beta\)-catenin which effects transcriptional events in the cell. GSK-3 also functions to modulate apoptotic events within the cell via protein kinase B (PKB) and PI3 kinase signalling, and inhibits glycogen synthase (GS) activity.
filaments (PHF) seen in Alzheimer’s disease. In addition to its association with the axin complex, APC also binds microtubules and when lost leads to chromosomal instability during mitosis.

### 1.4.2 Inositol phosphate signalling

Inositol monophosphatase (IMP) is the best known member of a super-family of structurally related PMEs that can hydrolyze all substrates with sugar phosphate backbones (Figure 1.3). Biochemical and structural studies of a number of family members, including IMP, inositol polyphosphatase (IPP), fructose 1,6-bisphosphatase and the rat 3′-phosphoadenosine 5′-phosphate PAP phosphatase (RnPIP), have found that this enzyme family contains a common amino acid sequence motif which constitutes a lithium-sensitive magnesium ion binding site. The magnesium ion is not required for direct hydrolysis of the phosphodiester bond, but is required for binding the cleaved product and phosphate. Lithium functions to trap the cleaved product in the active site, resulting in the uncompetitive inhibition of enzyme activity.

Inhibition of IMP reduces the cellular concentration of myo-inositol (Figures 1.4 and 1.5), which is required for the production of a spectrum of inositol phosphate-based soluble compounds and membrane lipids. The most studied of these is Ins(1,4,5)P₃ or InsP₃, an intracellular signal molecule that binds to receptors on the endoplasmic reticulum to release calcium, which in turn elicits a range of cell responses, including activation of protein kinases such as PKC. Lithium treatment would also be expected to affect other compounds, such as Ins(1,3,4,5)P₄ and InsP₆, which have signalling functions; PIP₂, which is hydrolyzed by phospholipase C to produce InsP₃ and diacyl glycerol (DAG), and a variety of phosphatidylinositides phosphorylated at the 3′ carbon, which form membrane-binding sites for proteins such as PKB.

Valuable insights regarding the mechanism of action of lithium have been gained using a single-celled eukaryotic amoeba, Dictyostelium discoideum.

![Figure 1.3](image) Structure of the sugar myo-inositol and its most well-known signalling derivative, inositol 1,4,5-trisphosphate (Ins(1,4,5)P₃ or InsP₃). Carbon atoms are numbered as indicated, showing the phosphorylation (‘P’) at carbons 1,4 and 5.
This research has identified mutants resistant to the effect of lithium – and one of these mutants, *lisA*, has an elevated InsP$_3$ concentration due to the up-regulation of multiple inositol polyphosphate phosphatase (MIPP) activity (Figure 1.4). This enzyme generates InsP$_3$ from an unconventional route, by the dephosphorylation of InsP$_{5-6}$. The *lisA* gene encodes prolyl oligopeptidase (PO), a cytosolic enzyme characterized by its ability to cleave peptides of less than 3 kDa at a proline residue. PO activity is important for brain function as its inhibitors enhance memory; lithium has the opposite effect on memory. This inverse relationship between PO activity and InsP$_3$ concentration has been demonstrated in mammalian neurons and cell lines derived from astrocytes, ancillary cells associated with brain neurons. Of particular interest is the association of abnormal PO activity with mood disorders and a number of other mental illnesses.\textsuperscript{37–39}
In addition to lithium’s effect on inositol phosphate metabolism, some PMEs, such as RnPIP and the *Saccharomyces cerevisiae* protein Hal2, can also efficiently dephosphorylate di-phosphonucleotide substrates, such as 3’-phosphoadenosine 5’-phosphate (PAP) and inositol 1,4-bisphosphate. In many cases the PAP phosphatase activity is the dominant enzyme activity. PAP phosphatase catalyzes the hydrolysis of PAP to form adenosine monophosphate (AMP). Lithium inhibition, therefore, may lead to increased PAP levels, which is a potent inhibitor of enzymes that utilize PAPs, such as the sulphotransferases. Loss of PAP phosphatase genes in yeasts causes dependence on exogenous sulphur and methioinone and inhibits RNA processing. This pathway is involved in the salt tolerance response in plants and fungi. It is not yet clear whether blocking PAP phosphatase contributes to the therapeutic action of lithium in the treatment of BD.

### 1.5 Lithium Therapeutics

#### 1.5.1 Bipolar disorder and schizophrenia

As described above, lithium inhibits GSK-3 and inositol phosphate signalling and both pathways have therefore been suggested to be involved in BD. The best current hypothesis describing how lithium functions in the treatment of BD is the

![Figure 1.5: Schematic graphs showing different modes of enzyme inhibition. The uncompetitive nature of lithium’s inhibition of IMP means that enzyme activity decreases with increasing lithium concentration, but at high substrate concentrations (low x-axis values) the inhibitory effect of lithium is stronger than that found in other forms of enzyme inhibition (competitive and non-competitive).](image)
‘inositol depletion’ hypothesis of Berridge et al. This theory suggests that the cause of BD may be overactive InsP signalling in the brain of these patients, and this may be reduced by the inhibitory effect of lithium on InsP signalling (Figure 1.4). In principle, therefore, lithium-based inositol-depletion effects should be reversed by addition of inositol to the test system, and this has been shown in many experiments. In vivo, it has been shown that lithium causes the suppression of rearing in rats, and this effect is overcome by intracerebroventricular injection of inositol. A more defined effect is seen with limbic seizures induced by pilocarpine, a compound that induces epileptic fits, which can be blocked by injection of lithium. Again, this effect can be suppressed by inositol. Using this ‘inositol rescue’ criterion, a number of brain physiological and behavioural effects of lithium have been ascribed to changes in InsP signalling. In reality, experiments using this ‘inositol rescue’ process are complicated by the fact that inositol uptake can be inhibited at high exogenous inositol levels, therefore causing similar effects to lithium treatment. Caution must therefore be taken when inositol addition fails to reverse lithium effects.

One way that scientists are trying to identify which of lithium’s targets is responsible for mood control is by examining other BD drugs to see if they also affect these targets. This has proved to be a contentious area of research. In support of the involvement of InsP signalling as the therapeutic target of lithium, researchers have found that all three commonly used BD drugs (lithium, VPA and CBZ) function to increase the size of neuronal growth cones, the developing tip of a mammalian neuron. This increase was shown to be overcome by the addition of inositol to these cells, thus implicating inositol depletion as the common mechanism of action of BD drugs. Furthermore, both lithium and VPA decrease the amount of inositol in the rat brain and change membrane lipid concentration, a process directly linked to inositol signalling. Indeed, a recent study in BD patients suggests altered InsP signalling may be corrected by both VPA and lithium, and these patients show altered activity of PO (see section 4.2), an enzyme which controls InsP signalling. The common effect of structurally diverse BD drugs on InsP signalling therefore strongly suggests this is the therapeutic target of these drugs.

The case for lithium acting on GSK-3 in the treatment of BD is weaker and centred around two sets of observations. First, inhibition of GSK-3 alters the structure of cerebella neurons. If a similar process occurred in other parts of the brain, e.g. the hippocampus and the frontal cortex, this could change brain function. Secondly, lithium is a neuro-protective agent, and can reduce the hypersensitivity to toxic insults seen in cells that overexpress GSK-3. It is therefore possible that lithium could protect against disease-induced cell death. Studies have shown that both bipolar and unipolar depressed patients show a decreased volume of prefrontal cortex grey matter, and this may be associated with a reduction in the number of glial cells, and reduced numbers of both glial and neuronal cells have been found in postmortem studies of these
patients. Lithium treatment has also been shown to increase the volume of grey matter in the human brain.

Interestingly, GSK-3 has been implicated in the origins of schizophrenia. Both the Wnt receptor Frizzled-3 (Fz3) and PKB protein have been associated with schizophrenia (Figure 1.2). Although the Fz3 association is only genetic, PKB polymorphisms have been found to directly reduce PKB expression. Treatment with the anti-psychotic haloperidol increases activity of the kinase PDK-1, an upstream activator of PKB. As PKB inhibits GSK-3 activity, these observations suggest that GSK-3 may be elevated in schizophrenic patients. Early reports on the use of lithium suggest that it may be active against schizophrenic patients, but with the availability of many anti-psychotic drugs it is not in common usage.

1.5.2 Alzheimer’s disease

Alzheimer’s disease is a neurodegenerative brain disorder causing neuronal dysfunction and ultimately cell death, giving rise to dementia. Its prevalence is increasing, as it was estimated to affect more than 10% of people over 65, or 48% of people over 85 in the US. The onset of Alzheimer’s disease occurs with the accumulation of extra-cellular senile plaques composed of amyloid-β (Aβ) peptides and with the accumulation of intercellular neurofibrillary tangles. Aβ peptides are composed of a mixture of mainly 40 and 42 amino acid peptides and are generated from the transmembrane glycoprotein amyloid precursor protein (APP) by sequential proteolysis catalyzed by aspartyl protease β-secretase (BACE) and presenilin-dependent γ-secretase.

There are several direct roles of lithium in treatment of Alzheimer’s disease. First, GSK-3 functions to phosphorylate Tau (section 1.4.1) – a process which is necessary for the accumulation of microfibrile tangles. Secondly, inhibition of GSK-α causes a reduced production of Aβ peptides. These processes are affected at therapeutic levels of lithium. A reduction of Aβ peptides is caused by the reduced processing of APP by γ-secretase, although it does not affect Notch processing, another signalling pathway modulated by this enzyme. Instead, lithium may function to modulate the access of specific substrates or the activity of these substrates towards the γ-secretase complex, a process linked to GSK-α signalling. Thirdly, some mutations of PS-1 are also associated with familial Alzheimer’s disease, and loss of PS-1 in mice leads to increased β-catenin protein and cell division; these results implicate PS-1 and GSK-3 in this disorder.

In addition to the direct involvement of GSK-3 in Alzheimer’s disease, the neuro-protective or anti-apoptotic effects of lithium may also play a role in the treatment of Alzheimer’s disease. The neuro-protective role of lithium can be clearly seen with regard to glutamate toxicity. Pretreatment of primary cerebellar granule cells with lithium gives a dose-dependent protection against this
toxicity, in a concentration range that is found in patients undergoing lithium treatment. This toxicity occurs via N-methyl-D-aspartate (NMDA) receptors, as antagonists to these receptors also block toxicity. It is interesting to note that this effect is unlikely to be a direct action of lithium, as pretreatment is necessary for protection\textsuperscript{59} and this effect occurs at even lower concentrations in cortically derived neurons.\textsuperscript{60}

In addition to glutamate, lithium has been shown to protect against induced apoptosis in neuronally derived cultures by a number of agents including the seizure-inducing compounds kainite,\textsuperscript{60} α-amino-3-hydroxy-5-methyl-\textsuperscript{4}isoxazole-4-propionic acid (AMPA),\textsuperscript{60} the anti-convulsants Phenytoin and CBZ\textsuperscript{61} and deprivation of high potassium and high serum.\textsuperscript{62} The broad range of compounds that lead to cell death suggests that a central signalling process is being activated in this apoptotic process and it is this common feature which is targeted by lithium. It is of considerable interest that VPA also functions to protect cerebella granule cells from glutamate excitotoxicity.\textsuperscript{60} This suggests that inositol trisphosphate depletion, which is the common action of the mood stabilizers, lithium and VPA,\textsuperscript{36} may function to prevent cell death through excitotoxicity. In support of this, pretreatment of both cerebella granule cells and cortical neurons with lithium for 7 seven days reduces the NMDA-receptor-mediated Ca\textsuperscript{2+} entry into cells, but does not change subunit levels.

Glycogen synthase kinase-3 may act as a modulator of apoptosis. Treatment of rat hippocampal neurons with the Aβ peptide, which builds up in patients with Alzheimer’s disease, both increases GSK-3β expression and induces apoptosis.\textsuperscript{63} The apoptotic effect is blocked by antisense oligonucleotides directed at GSK-3. Wnt stimulation also protects against apoptosis, although this may be due to indirect induction of insulin-like growth factor (IGF) proteins. Insulin, IGFs, nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) can all inhibit GSK-3 through activation of PI3 kinase (Figure 1.2). Inhibition of PI3 kinase, by use of chemical inhibitors or serum withdrawal, leads to increased GSK-3 activity, and this correlates with apoptosis. In addition, full GSK-3 activity requires phosphorylation at an internal tyrosine (Tyr216).\textsuperscript{64} Interestingly, it has been shown that several apoptotic stimuli induce an increase in Tyr216 phosphorylation and increase GSK-3 activity. Consistent with these observations, overexpression of GSK-3 also correlates with neuronal degeneration.\textsuperscript{65} Moderate increases in GSK-3 activity in human neuroblastoma SH-SY5Y cells did not increase the basal rate of apoptosis or caspase-3, which sits within the apoptotic signal transduction pathway, but they are associated with increased sensitivity to apoptotic stimuli. These effects are blocked by expression of the anti-apoptotic protein Bcl-2 and expression of a dominant negative form of a tumor suppressor p53. Consistent with a role of GSK-3, many of these effects can be reduced by lithium treatment.

Lithium also functions as a neuro-protective agent by altering gene transcription. P53 promotes the expression of Bax, which is a pro-apoptotic gene
whose product may cause the release of cytochrome c from the mitochondria and induce subsequent caspase activation and protein degradation. Long-term lithium treatment increases p53 expression in cerebellar granule cells, as are Bax mRNA and protein levels. Similarities, the protein of the Bcl-2 gene is a cytoprotective protein, which interacts with the mitochondrial membrane to prevent Bax-induced cytochrome c release and the induction of this apoptotic pathway. Long-term lithium treatment increases both Bcl-2 mRNA and protein levels. This has also been reported in rat brains following treatment with either lithium or VPA.

1.5.3 Ischemia (stroke)

Animal models of stroke have been extensively used to examine possible therapeutic effects of lithium. Pretreatment of mice for 16 days prior to stroke induction greatly reduces the damage caused by middle cerebral artery occlusion (MCAO) which is the cause of brain damage. This neuro-protective effect is also seen in a model of stroke which has been suggested to more closely resemble acute stroke cases, that is, transient ischemia models of stroke. In this system, animals are exposed to MCAO for 1 h, with reperfusion immediately afterwards. Administration of a single dose of lithium up to 3 h after this transient exposure significantly reduces the damage caused by this process. It is interesting that this protection does not require extended pretreatment, which may suggest a separate mechanism of protection to the neuro-protective effects discussed earlier. In addition, the apoptotic effects of lithium (p. 13) also may protect brain regions post stroke, as lithium decreases Bax protein levels in this transient model by around 70%.

1.5.4 Adverse effects

The narrow therapeutic window of lithium makes monitoring blood levels essential during treatment. Increasing lithium blood levels over 1.2 mM gives rise to tremors – usually noticed in the fingers – and dosage reduction can usually reduce this effect to mild tremors. Some patients complain of slowed mental agility and forgetfulness. Memory problems are one of the leading causes of non-compliance and the third most common side effect. Extreme lithium doses produce chronic nausea and diarrhea; thus lithium poisoning is rare, but is sometimes seen after poor monitoring of clinical application or an unsuccessful suicide attempt. In a study of 15 deliberate self-poisonings, no deaths were seen, although as discussed in section 1.3.1, the lithium-induced deaths of the 1950s clearly show that some individuals are at risk. Episodic nausea can usually be relieved by taking lithium with food. Some patients gain weight progressively on lithium and it is the second most common reason
patients stop taking it. Weight gain is greater in patients who are overweight to begin with. Some patients show decreased thyroid levels and rarely goiter. About 5% develop hypothyroidism and 30% have elevated thyroid-stimulating hormone levels. Polyuria (passing an excessive quantity of urine) or polydipsia (excessive thirst) occurs in one out of five patients. Aggravation of psoriasis and alopecia can occur but hair usually re-grows with or without the lithium.

Based on reports from the 1970s, kidney damage has been a concern for patients taking long-term lithium treatment. However, this worry has not been borne out in further study of correctly treated patients and in practice there appears to be a low incidence of renal damage, although kidney examination is recommended every 6–12 months. Harm can occur if patients are stabilized on lithium and given drugs which may affect renal balance. For instance, non-steroidal anti-inflammatory drugs can cause a 60% increase in blood lithium concentration because of their effect of reducing lithium clearance through the kidneys. These drugs can cause a doubling of the blood lithium levels and the patient may therefore show lithium toxicity. This can also occur with anti-inflammatory drugs like Ibuprofen®, Naproxen® and Indomethacin®.

Acknowledgements

R.S.B. Williams and A.J. Harwood are supported by a Wellcome Trust Career Development Fellowship and a Wellcome Trust Senior Fellowship, respectively.

References


16 Lithium Metallotherapeutics
References
