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# SELECTIVITY AND UPTAKE OF LITHIUM

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# SELECTIVITY AND UPTAKE OF LITHIUM

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**Lithium salts are widely utilized as psychopharmacological agents for the therapy of bipolar disorders and related illnesses. Although it is readily bioavailable and has just a single biologically relevant oxidation state, its biological activity remains poorly understood. This comment will examine several key issues in this area: 1) Given the chemical properties of lithium, how do ion transport and metal-dependent enzymes mediate the selectivity of lithium and other alkali ions? 2) Is it possible to predict which magnesium-dependent enzymes can be inhibited by lithium? Answers to these questions are now accessible because of the recent structural determinations of ion channels and of magnesium-dependent, lithium-sensitive inositol polyphosphate 1-phosphatase. This comment will attempt to synthesize the dispersed coordination chemistry data for lithium which can help us evaluate these potential targets for lithium therapy**

Keywords: lithium, magnesium, ion channels, selective inhibitor

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## INTRODUCTION

Lithium is a fascinating chemical and biological oddity. In spite of its toxicity, it is one of the most efficient and important drugs for treating bipolar disorders. It is the lightest and smallest metal, with just a single biologically relevant oxidation state. Nevertheless, numerous biological roles have been attributed to lithium, such as an inhibitor of presynaptic neurotransmitter-regulated release,[1] of postsynaptic receptor regulation,[2] and of signal transduction cascades.[3,4] These effects are associated with neural gene expression and neuroplastic changes, and thus lay the basis for its clinical biochemistry. Nearly two centuries after the recognition of elemental lithium, it is now being used to treat a multitude of diseases. Remarkably, the key discoveries of its use as a mood stabilizing agent were only noticed by John Cade in 1949,[5] and studied by Mogens Schou in the early 1950s.[6]



In order to better understand the diverse therapeutic effects of such a simple ion, this article will collect and integrate our understanding of lithium's coordination chemistry and its emerging biochemistry. Although lithium transport and distribution were thoroughly investigated during the late 1970s, more recent research has examined its interactions with specific sites within post-synaptic receptors. From 1990 and onwards, progress in genetics, molecular biology, and protein crystallography allows us to systematically apply the lessons of lithium's coordination chemistry to understand lithium drug action and biochemistry. In the process, we seek to evaluate lithium's transport properties, and compare them to similar cations such as potassium, sodium, magnesium, and calcium. Herein we attempt to answer two questions: how specific is lithium's ability to bind to and be transported through membrane selective pores? And, is its interaction with magnesium binding sites the origin of its therapeutic mechanisms?

## LITHIUM'S BIOAVAILABILITY

Lithium (0.006%) is more abundant than lead, tin, gold or silver in the earth's crust, and it is found as salts associated with quartz and mica in pegmatite deposits.[7] Seawater also contains 0.0001% lithium, and some brines may contain several thousand times more lithium. The latter are therefore useful sources of lithium salts, such as Searle's Lake in California, and the Great Salt Lake in Utah. Lithium is thus widely dispersed in nature and readily bioavailable. Not too surprisingly, lithium

is also present in most human organ tissues, including the brain, bones, teeth, kidney, lung, spleen, liver, muscles, gut, and skin. Traces of lithium are found in human blood, bile, lymph and urine. Although some plants such as *Thalictrum* sp. and *Cirsium* sp. accumulate lithium, it is not recognized as an essential mineral in plants or animals. Thus whether the observed traces of lithium described above are non-adventitious, and thus due to as–yet–unknown metabolic functions, remains unclear.

## ION TRANSPORT

Cellular localization of lithium is mostly done by using $^{7}$Li NMR (I = 3/2) and atomic absorption spectroscopy ($\lambda_{abs} = 670.8$ nm). However, it is quite difficult to study the lithium cation because of its high mobility and the interference of related metals present in large amounts. In $^{7}$Li NMR spectroscopy, lithium has a long lattice relaxation time (*in vivo*, $T_1 = 2$–8 s for $^{7}$Li, as compared to 10–50 ms for $^{23}$Na), so the $^{7}$Li measurements are less efficient.[8] The more serious limitation is low sensitivity. For equal numbers of atoms, the sensitivity of $^{7}$Li is 27% that of $^{1}$H. Hence, $^{7}$Li Magnetic Resonance Imagery can only give gross spatial variations in concentrations, and not cellular or molecular features.

Lithium flows into cells mainly through passive diffusion; excretion is through the sodium-lithium counter transport pathway. Ion channels, such as voltage-sensitive sodium channels and Na,K-ATPase, accept the lithium ion as a substitute for their normal ionic substrates.[9] Therefore, lithium transport is closely related to those of sodium and potassium, and so is the chemistry.

Lithium, sodium and potassium belong to the family of alkali metals (group 1), which are found almost entirely in monovalent ionic form. As a monovalent cation, it is small and hard but in water it establishes a large hydration sphere[7,10] (Table 1) and is the least reactive of the alkali

**Table 1.** Mono- and Di-valent alkali and alkaline earth metals contrasted

| | Li | Na | K | Mg | Ca |
|---|---|---|---|---|---|
| Ionic radius (Å) | 0.60 | 0.95 | 1.33 | 0.65 | 0.99 |
| Charge density | 1.11 | 0.28 | 0.10 | 1.74 | 0.49 |
| Hydrated radius (Å) | 3.40 | 2.76 | 2.32 | 4.67 | 3.21 |
| Hydration energy (kJ mol$^{-1}$) | −498 | −393 | −310 | −1900 | −1565 |

**Table 2.** Water exchange rates in $s^{-1}$

| $Li^+$ | $Na^+$ | $K^+$ | $Mg^{2+}$ |
|---|---|---|---|
| $5 \times 10^{-8}$ | $1 \times 10^{-9}$ | $1.5 \times 10^{-9}$ | $1 \times 10^{-5}$ |

metals. The atomic and ionic radii of lithium and magnesium are quite similar. Lithium and calcium have the same electronegativity. The hydrated sphere and polarizing power of lithium lie between those of magnesium and calcium. So lithium may interact with magnesium and calcium–dependent biological processes. The reactivity of lithium can be related to the reactivity of magnesium through the "diagonal relationship."

In Table 2, we can see that $K^+$, $Na^+$, and $Li^+$ have roughly the same water exchange rate. This provides further evidence for similar behavior of lithium to these cations in terms of transport. Therefore, the lithium ion may be a substitute for the normal ionic substrates of ion channels. Hence, insight into ion channels would help us to understand those ion flows.



## Influx through Ion-channel Pores

How does the cation flow through the channel, either in or out, and how does the channel select the right ion? Unfortunately, the complete structure of an ion channel has not been fully determined, and the two main techniques to study them are site-directed mutagenesis and X-ray diffraction of crystallized proteins. Although a voltage-gated potassium channel has been crystallized, PDB, 1BL8,[11] the sodium channel has not. These channels are composed of 4 domains, each having 6 transmembrane segments (S1-S6) connected to each other by loops. The S6 segment defines the inner vestibule of the pore. The loop between S5 and S6 dips back into the membrane. The combination of those four loops, one from each domain, forms the selective filter for the pore (Figure 1).[12]

Potassium channels from *Streptomyces lividans* (KcsA channel) have three identified binding sites for potassium.[13] The selectivity filter, a narrow funnel delimited by a first and second binding site,[14] is 3 Å in diameter and 12 Å long, and is lined with backbone carbonyl oxygen atoms.

*In the Potassium Channel Vestibule.* How does the potassium channel mediate the transfer from a hydrated state in the cellular medium to

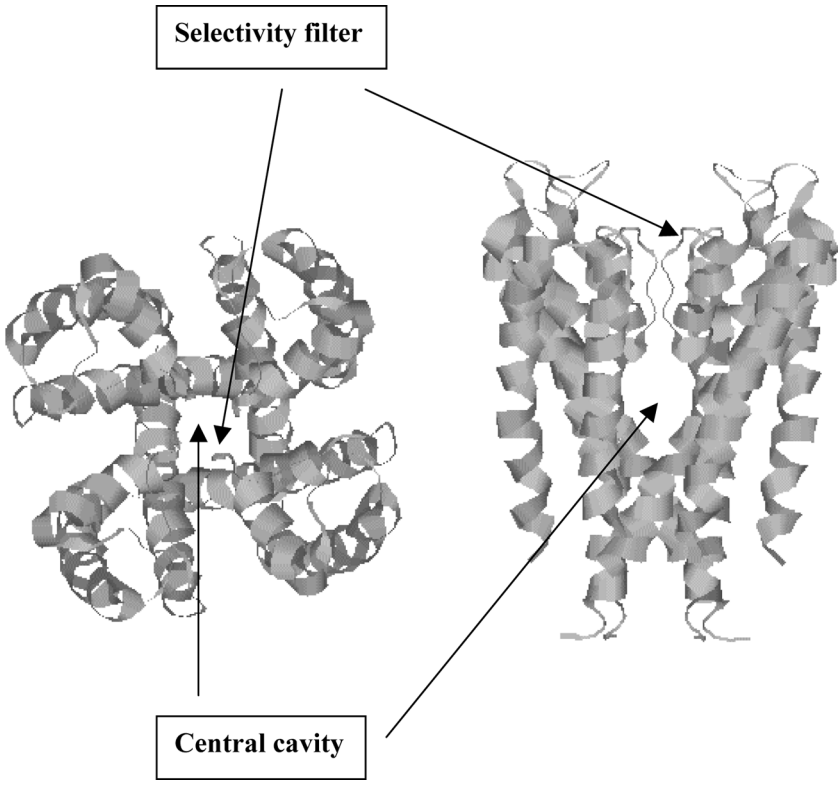


**Figure 1.** Two views of the KcsA potassium ion channel membrane protein from the Protein Database entry 1BL8. The peptide backbone is shown as a ribbons representation with the selectivity and the central cavity shown for clarity.

a dehydrated state in the selective filter? At the central cavity, eight water molecules, forming a square antiprism geometry, surround the potassium ion. The potassium complex is attracted by electrostatic interactions with four carboxylate oxygen atoms from the Gly79 residues, directed straight out into the extracellular medium. Positioned on the pore axis, the potassium loses half of its hydration shell by complexing with the oxygen atoms (Figure 2). Just beneath the protein surface, carboxylate pairs formed by the side chains of Glu 71 and Asp 80 provide four extra negative charges near the entry way. They attract the potassium, and enable its diffusion into the channel inner pore in less than a few hundred picoseconds.[13] Here it becomes fully dehydrated. The hydration state of the metal ions depends significantly on the conformational flexibility of the

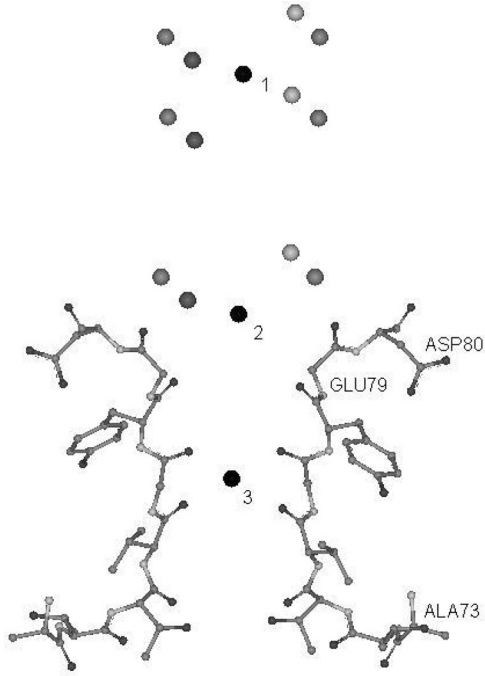


**Figure 2.** Potassium ion dehydration and selection by the selectivity filter in KcsA. The potassium ions, in dark, are shown in three sites, 1–3, in successively lower degrees of dehydration upon entry into the selectivity filter with the oxygen of the water and protein shown in light grey.



channel. In the selective filter the cation is surrounded by eight oxygen atoms arranged in exactly the same geometry as the water molecules. Therefore, the energy lost by the dehydration is recovered. Moreover, stepwise dehydration minimizes the energy barrier for cation entry in the channel.[15] The $K^+$-O coordination distances range from 2.70 to 3.08 Å.

Is the geometry of this potassium complex often encountered in potassium salts? Potassium is indeed found mostly eight coordinated. For example, in the ($CaKAsO_4 \cdot 8H_2O$) salt, the complex $[K(H_2O)_8]^+$ has square antiprismatic geometry.[16] In the Cambridge crystallographic data base, CCDB, most structurally characterized potassium complexes correspond to crown ether complexes. The observed K-O distances are roughly between 2.7 and 3.0 Å for six-coordinated complexes. Thus the

model proposed in the potassium channel is consistent with known inorganic crystals. However, we could not find 6- or 8-coordinated potassium complexes bound to carboxylates in the CCDB. Six-coordinated potassium complexes often have carboxylate ligands, but no examples exist for the 8-coordinated potassium complex.

*Na,k-ATPase Channel.* As the Na,K-ATPase channel structure has not yet been crystallized, and the structure solved, only homology–based models are available. These models suggest that there are 2 binding sites for potassium and 3 binding sites for sodium in this channel. For example, Ogawa and Toyoshima[17] showed very regular coordination geometry for potassium in their homology model. Surprisingly, six oxygen atoms are involved, and not eight, oriented about 2.7 Å from $K^+$. In one site, they all come from protein residues. In the other, one oxygen atom belongs to a water molecule (Figure 3). These predictions correlate well with the crystallographic data for sodium salts in which the sodium ions are typically six coordinate, and the preferred geometry is that of a distorted octahedron. The salt ($Na_2SO_4 \cdot 10H_2O$) has such a representative octahedral $[Na(H_2O)_6]^+$ geometry. However, some predictions from this model are at variance with known sodium ion chemistry. For example, the sodium site II is seven-coordinated and not six. Bond valence models[18] have been used to evaluate the possible binding sites of the cations,[19] and this requires an empirical formula developed by Brown to predict the positions of atoms in complex crystals.[18–20] However, Brown restricted his model to simple inorganic compounds, and contended that most organic and metallic compounds do not fit the model.[20] Indeed, data used in the models parameterization are all given by small inorganic crystals, which may not be applicable to biological systems. Protein tertiary structure often constrains the geometries of individual sites which, unlike metallic crystallized salts, cannot easily minimize the energy of a single site. Moreover, proteins often exhibit dynamic conformational structures, with their crystal structures being a single representation. These structural alterations are very likely when cations bind to them. Moreover, although proteins are in an aqueous medium, the selective filter is not thought of as an aqueous potassium channel. So, how valid is the bond valence model for predicting the binding sites for cations? Have there been verifications of its consistency? Neither question seems to have been rigorously tested and a note of caution needs to be raised with the models spreading use in biochemistry.

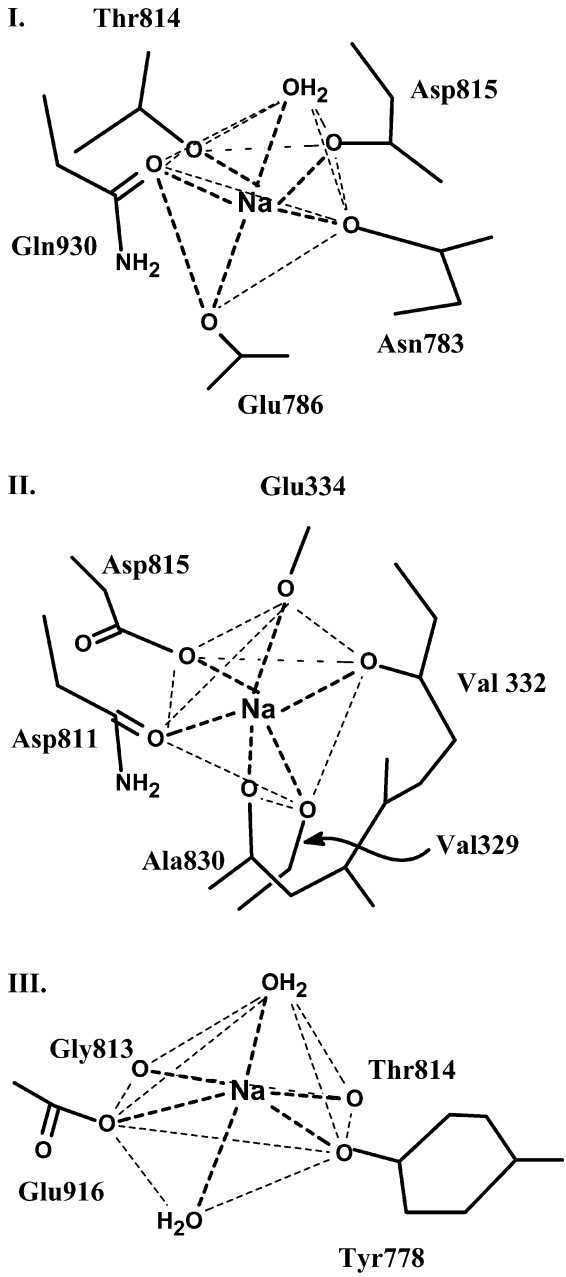


**Figure 3.** Homology predicted coordination geometry of sodium and potassium in $Na^+$, $K^+$-ATPase. Images from Ogawa and Toyoshima, ref 17.

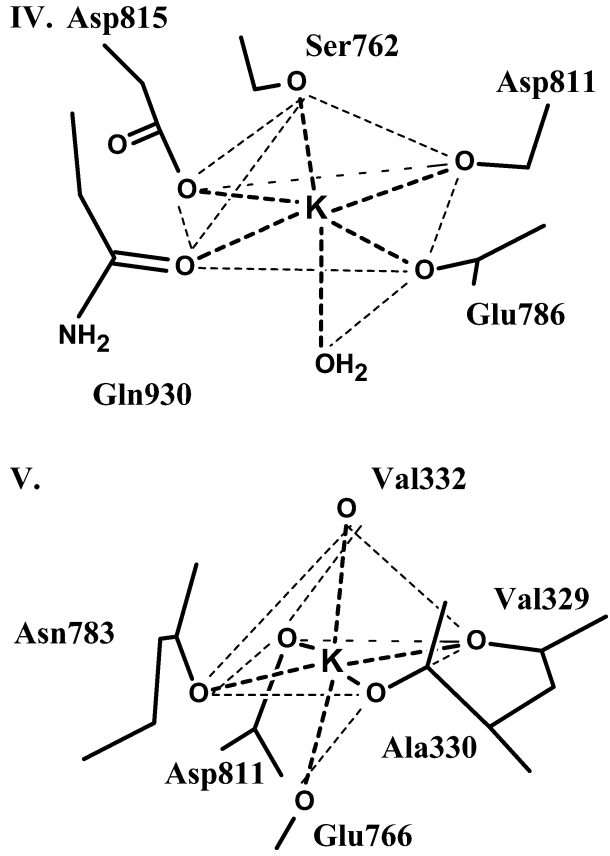


**Figure 3.** Continued.

*Selectivity.* Chemical model systems to study selectivity are macromolecules such as cryptands and crown ethers. Potassium is bound selectively by 18-crown-6, for which sodium is too small, and [2.2.2] cryptand (Figure 4).[21] For sodium, the ligand is dicyclohexyl-16-crown-5 and [2.2.1] cryptand (Figure 5).

The size appears to be the first feature for selectivity, as the above macromolecules show. The structure of the pore, apart from the size, due to the disposition of the carboxylate and amide oxygens, selects the right ion. While the geometry created by the eight oxygen atoms in the selectivity filter is perfectly similar to the hydration shell for potassium, it is not the case for sodium. Indeed, $Na^+$ is too small to fit

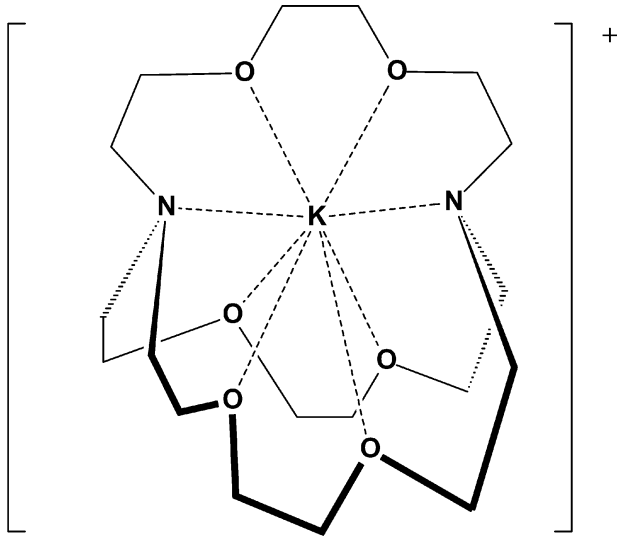


**Figure 4.** Potassium bond in [2.2.2] cryptand.



perfectly in the selectivity filter. Thus, unlike potassium, the energetic barrier for dehydrating sodium is not compensated as is found for potassium. As a result, the potassium channel is very permeable to potassium and hardly to sodium.

Another factor influencing the selectivity is the hydration state. It seems that the more hydrated the ion, the less selective is the channel. Since the proposed sodium channel has a hydrated layer, it is less selective than is the potassium channel. A water-filled cavity contributes significantly to the stabilization of ions by electrostatic effects.[22] The energy barrier for the ion to overcome would also be smaller because water ligands can very easily be exchanged.

## Therapeutic Effects of Lithium

Lithium carbonate (bipolar disorder treatment), lithium oxalate (anticoagulant), citrate (antidiuretic, antirheumatic), lithium fluoride (radiation therapy), and lithium chloride (hypertension treatment) are used in medicine.[5] Serious side effects have been recorded, especially for lithium chloride in the 1940s. Lithium was considered a dangerously poisonous substance in the 1950s. Side effects at low serum lithium concentrations

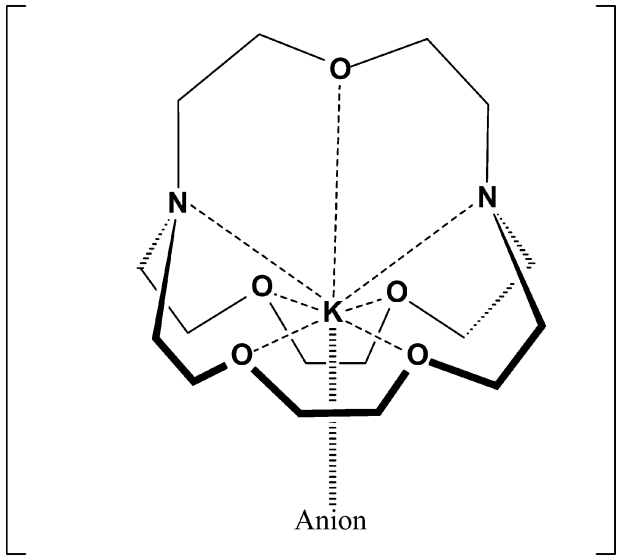


**Figure 5.** Potassium binding to the smaller cavity in the [2.2.1] cryptand.



are gastrointestinal irritation, tremor of the hands, thirst, and polyuria. Concentrations above 2 mmol/L are termed, which can result in heart and kidney injuries, and severe and protracted impairment of consciousness.[23]

Lithium is very likely to act by competing with magnesium for its binding sites. As magnesium has a critical role in many biological processes, lithium's alteration of magnesium activity may affect many functions, particularly the signaling pathways. Indeed, during the manic periods of bipolar patients, higher concentrations of myo-inositol have been detected.[23] Treatment with lithium is efficient in this disease, because it leads to a normalization of the myo-inositol concentration.[23] It is thought that lithium inhibits a phosphatase in the phosphoinositol signaling pathway (Figure 6). This enzyme, inositol monophosphatase (IMPase, PDB code 1IMD), requires magnesium as a cofactor. Lithium is shown to be able to inhibit it uncompetitively in vitro at a $K_i = 0.8\,\text{mmol}\,L^{-1}$ within the therapeutic range for lithium treatment of patients with bipolar disease.

Therefore, how likely it is that lithium fits in magnesium binding sites? Although the Protein Data Bank has the crystal structure of

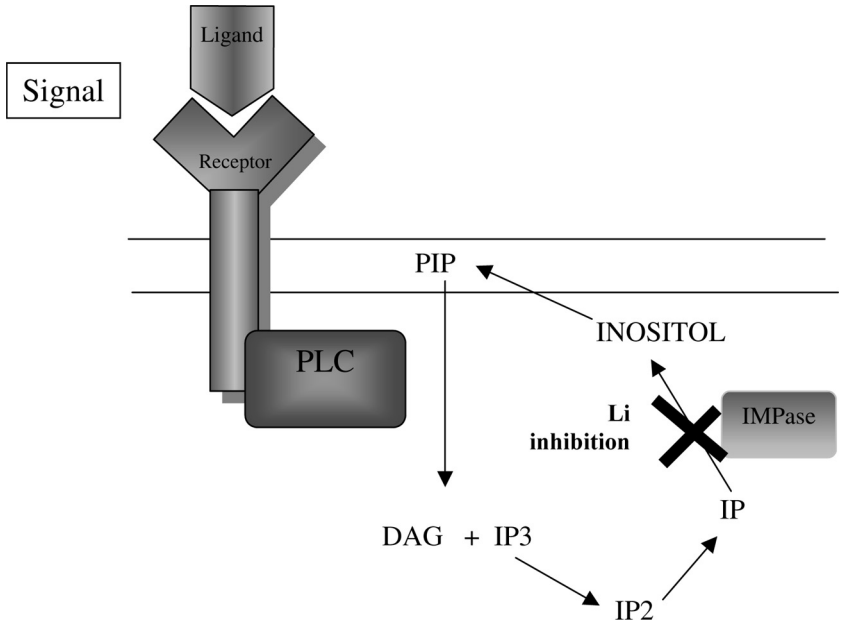


**Figure 6.** Inositol depletion hypothesis: Ligand binding to a surface receptor activates phospholipase C (PLC), which hydrolyses the phospholipid PIP2 to yield second messengers diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3). Inhibition of IMPase with lithium depletes inositol, therefore PIP2, and consequently IP3 and DAG, thus indirectly inhibits transmembrane signalling.



IMPase,[24] it was not crystallized with magnesium. Hence, we do not have data on the magnesium binding sites of this enzyme. However, a crystal structure of another protein from the same magnesium/lithium sensitive family, inositol polyphosphate 1-phosphatase (IPPase, PDB code 1INP), has correctly reconstituted magnesium.[25] They share a similar, highly conserved common core structure,[26] which is essential for metal binding and consequently for catalytic activity. They have an identical metal–dependent and lithium–sensitive catalytic mechanism. So studying the active-site pockets of IPPase would give us a fairly good idea of those in IMPase, since the major difference lays in residues involved in their specific substrate recognition, not in their magnesium binding domains.

There are 2 binding sites for magnesium, with distorted octahedral geometries, which is a common geometry for magnesium (Figure 7). Each

metal is complexed to a $\eta^2$-carboxylate ligand (Mg1: Asp 153. OD 1 and 2, Mg2: Asp 54.OD 1 and 2). However, the atoms (Mg–O–C–O–) are not coplanar, since the torsion angle is nonzero. Two oxygens (from $H_2O$ 447 and Asp 153, OD1) also bridge the magnesium ions, which are 3.88 Å apart. There is also a substantial distortion of the octahedral structure, which may be particularly important to the first site, as this disortion creates a large hole, other ligands are too far away, >10 Å, to interact with metal. This unfilled space may be where the substrate of the enzyme binds to the metal. The average Mg-O bond lengths for both sites are very long: 3.37 Å for site 1, and 3.24 Å for site 2.

To gauge how variable the Mg–O bond lengths are within proteins we examined the 1128 magnesium binding proteins registered in the Protein Structure Data Bank. We analyzed 9 proteins whose crystal structures have the highest resolutions, typically <1.6 Å, so the distance information is the most readily contrasted with small molecule crystallographic results.



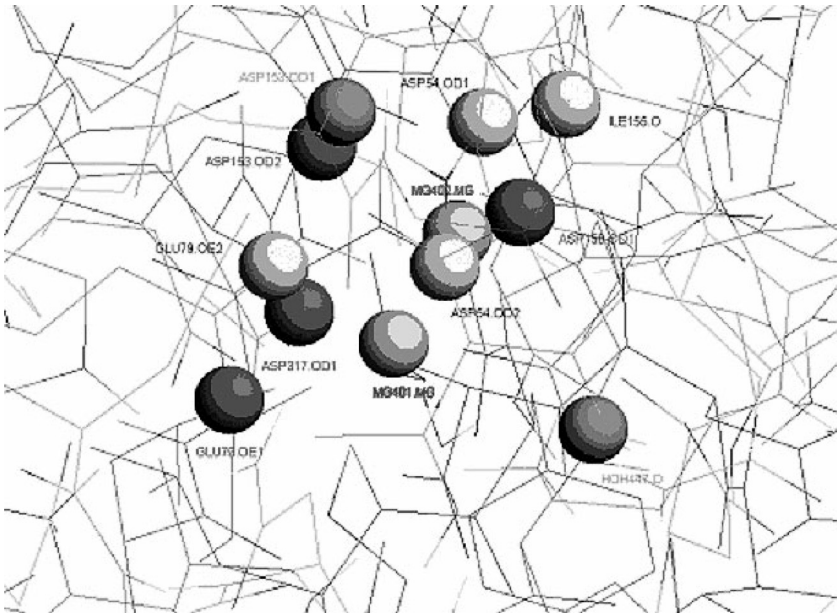


**Figure 7.** IPPase has two magnesium binding sites. The four peptidic oxygens, which are thought to be complexed to the magnesium1, are shown in dark grey and the four which are bound to magnesium2 in light grey. The shared bridging oxygens are shown in grey.

Chart 1 shows that shorter bond lengths are preferred (eg. 2.1 Å), but there is a significant frequency of bond lengths at about 3.4 Å. So, the distances proposed for our magnesium complex are often encountered in proteins. Ideally the same analysis should be performed on lithiated proteins, but the electron density of lithium is so low that it is seldom exactly located and refined in protein crystallography. We have, however, compared these to general inorganic compounds available in the CCDB containing lithium and magnesium complexed to oxygen. There are 142 different lithium complexes and 250 magnesium complexes, which are more than 6-coordinate. We can see in Chart 2 that lithium prefers longer metal-ligand bond lengths than magnesium. This can be easily understood, since magnesium is divalent while lithium is monovalent.

Thus, lithium may compete for the binding site because it fits better inside the site (longer metal-ligand bond length). Or it may also form a tetrahedral complex, instead of an octahedron, especially for the second binding site, which is smaller. The distribution of observed lithium-oxygen distances in CCDB entries as a function of coordination number is shown in Chart 3.



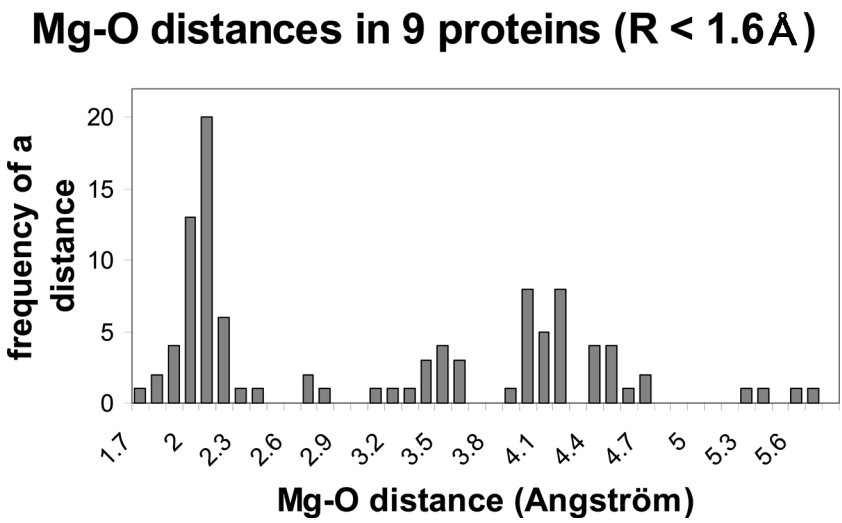


**Chart 1.** Distribution of Magnesium–Oxygen bond lengths from nine high resolution structurally characterized magnesium dependent proteins. Protein data base codes: 1MUW, 1M15, 1JM1, 1QL0, 1KJQ, 1KQP, 1MNZ, 1K4I, 2TPS.

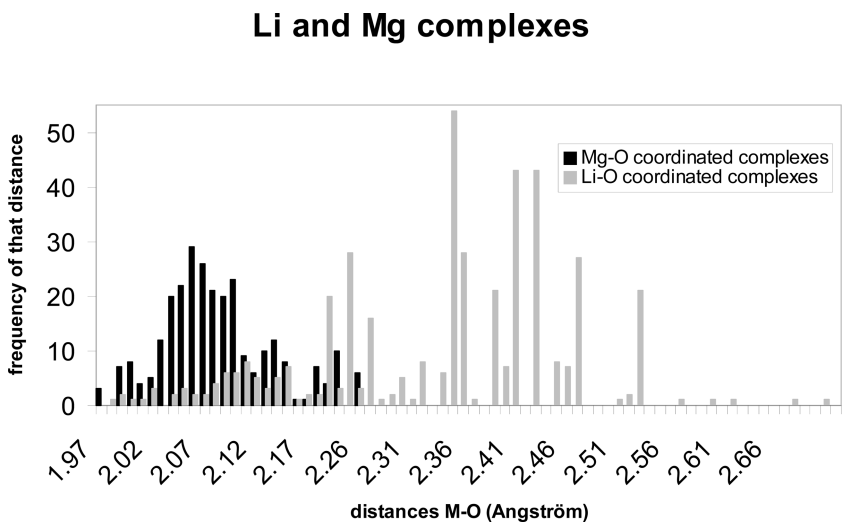


**Chart 2.** Distribution of lithium–oxygen and magnesium–oxygen bond lengths from the Cambridge Crystallographic Data Base.



Having a clearer idea of how lithium is able to compete with magnesium, we tried to understand the way lithium could inhibit the enzyme. The commonly proposed mechanism of inositol phosphatase activity involves both magnesium ions. The first magnesium, after binding to the enzyme, recruits the substrate, probably to the empty space found at the active site. The second magnesium then binds to the protein. Both magnesium ions are bound to the water molecule 447, making it acidic enough to generate a nucleophilic hydroxide, which can then attack the phosphate-ester bond of the substrate. The phosphate of the substrate is then cleaved.

Lithium is thought to bind to the second site, after the substrate is already bonded to the active site. Since lithium is less electron-withdrawing than is magnesium, the water molecule may not be sufficiently activated to promote dephosphorylation.

## CONCLUSION

In this article, we have investigated how selectivity is achieved by ion channels, and how lithium is able to compete with magnesium in a metal-dependent enzyme. Chemical characteristics of those cations partly explain their biological behavior. However, further studies coupling the

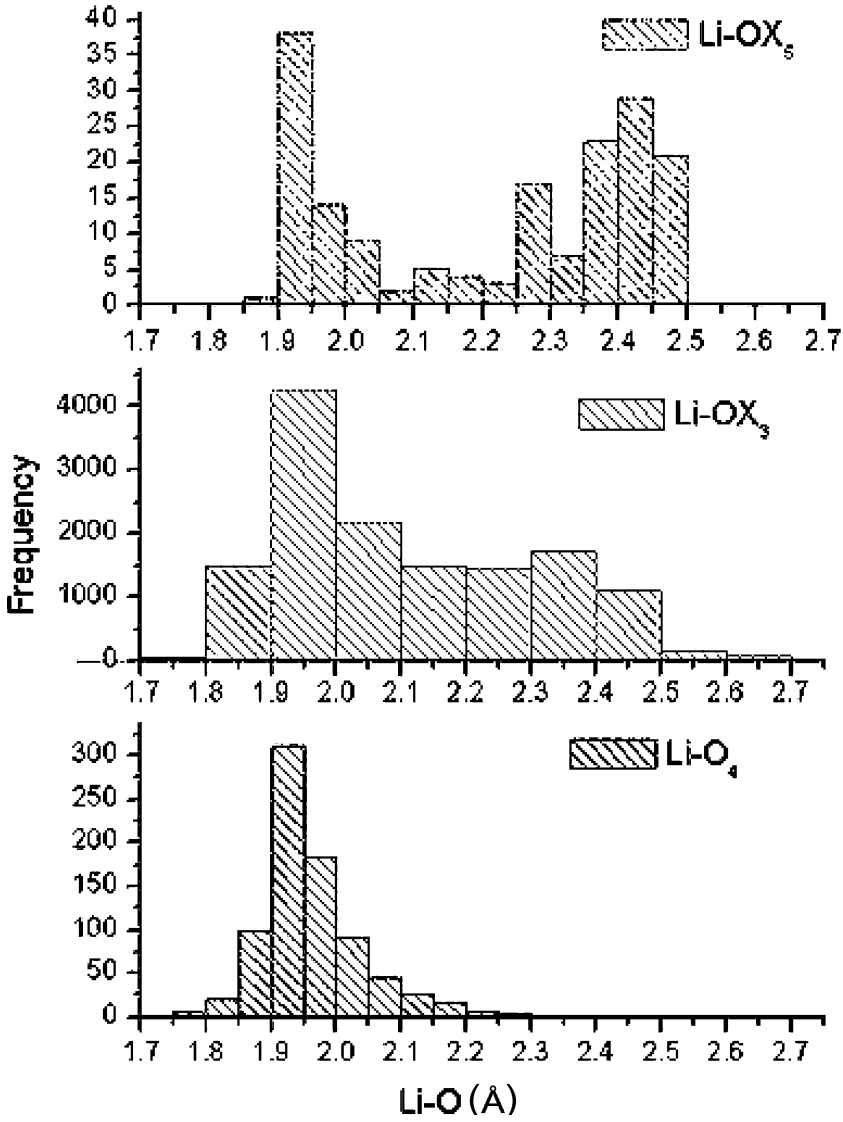


**Chart 3.** Distribution of lithium-oxygen bond distances as a function of coordination number for entries in the CCDB.

chemistry of lithium to biological processes should be made. Among other possibilities, designing probes for lithium or better tools to simply localize lithium in cells would be of great help to understand the action of this small ion in biology.

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