Structural studies on IMPase, the target of the mood-stabilising drug lithium

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IMPase (Myo-Inositol Monophosphatase) is the target of lithium therapy for Bipolar Disorder, a disease that affects 1% of the population worldwide [1]. Lithium has a small therapeutic range of concentrations before it becomes toxic, and it is also known to cause severe side effects. Bipolar patients show high levels of inositol presumably due to overactivity of IMPase.

The aim of this project is to determine the precise binding site(s) for lithium ions (see Figure 1, [2]) and thereby detail the mechanism by which IMPase is inhibited. The studies will involve determination of the neutron structure of bovine IMPase with lithium bound, to define the protonation states of active site groups and to identify the physiological metal-binding sites. Since lithium ions do not scatter x-rays strongly, the neutron studies will allow us a much improved definition of the lithium binding sites than could be achieved by x-ray analysis. The structural information from neutron diffraction aim to facilitate the design and development of better therapeutic agents for bipolar disorder.

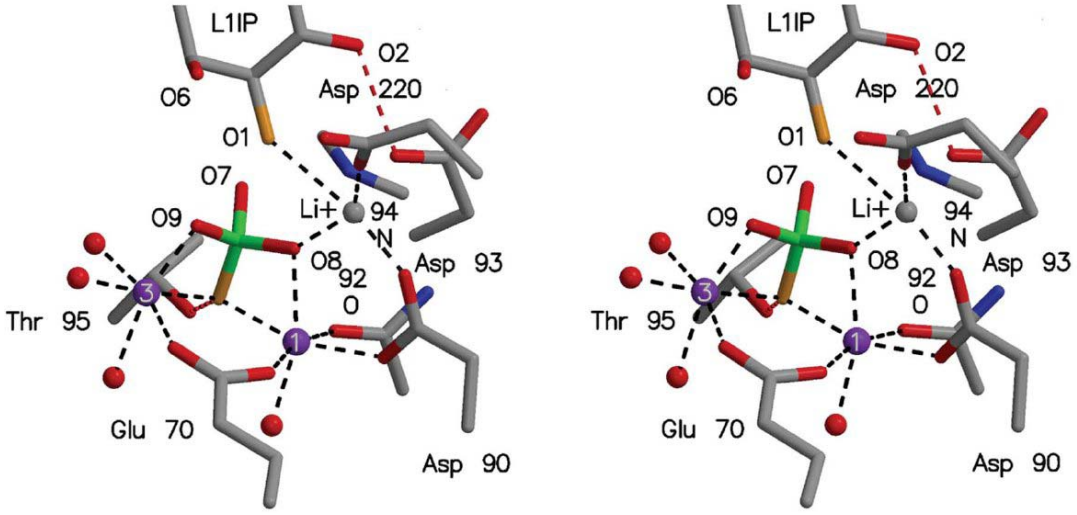

Figure 1: Modelling of the lithium-inhibited IMPase structure based upon that of the yeast Hal2p PAPase–2Mg^{2+}–AMP anion–Li^{+} complex [3], in which the tetrahedral coordination of Li^{+} has been inferred. Replacement of Mg^{2+} by Li^{+} prevents the protonation of the inositolate group after phosphoester hydrolysis, trapping inositolate and monophosphate in the active site and effectively inhibiting the enzyme (Figure taken from [2]).

References

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