GTP-binding proteins

Lithium affects G-protein receptor coupling

Alan H. Drummond

SINCE their discovery almost 40 years ago by Cade, lithium salts have been used effectively in the treatment of mania. It remains a mystery how a simple metal ion can exert such a profound psychopharmacological effect in the relative absence of systemic side-effects. The two theories that best explain the effect of this ion depend on the perturbation of the intracellular signalling molecules used by neurotransmitters: inositol lipid-derived mediators and cyclic AMP[1]. On page 440 of this issue[2], Avissar *et al.* report that lithium, at therapeutic concentrations, can alter the function of a core feature of both of these signalling systems, namely GTP-binding proteins.

A substantial proportion of the body's different cellular receptors transmit their information into the cell by virtue of their ability to activate a relatively small, but growing, number of GTP-binding proteins[3]. Although various agents that can perturb G-protein function are known — for example, cholera and pertussis toxins and forskolin — little attention has been paid to the possibility that lithium ions might exert their therapeutically relevant effect at this site. Nevertheless, it has been evident for some time that the ion has the ability to affect G-protein-dependent phenomena such as receptor-activated inositol lipid metabolism and adenylate cyclase. Occupation of appropriate hormone and neurotransmitter receptors by their agonists leads to an exchange in the guanine nucleotide bound to the target G-protein such that GDP is replaced by GTP. Such changes can be monitored both by examining agonist-dependent changes in GTP binding and, more routinely, by monitoring the guanine nucleotide-dependent decrease in the affinity of the receptor for an agonist.

Inhibition

Avissar *et al.*[2], using both approaches, show that lithium can inhibit the coupling of both muscarinic cholinergic and β-adrenergic receptors to pertussis toxin- and cholera toxin-sensitive G-proteins, respectively, and that the concentration of lithium that exerts this effect (0.6 mM) is within the therapeutic range. Animals treated chronically with lithium show a similar effect that is reversible within 48 hours. The authors suggest additionally that this effect could explain recent data indicating an inhibition by lithium of both cyclic AMP formation and of the accumulation of inositol tetrakisphosphate ($InsP_4$), one of the many inositol phosphates that are formed following receptor-stimulated inositol lipid hydrolysis[4,5].

The most puzzling aspect of the ability of lithium to ameliorate the manic-depressive condition is its relatively selective action upon the central nervous system. In 1982, Berridge, Downes and Hanley proposed[6] that lithium acts by interfering with neurotransmitter-stimulated inositol lipid metabolism. This hypothesis followed the pioneering work of Allison, Sherman and their collaborators (recently reviewed in ref. 1) who reported that inositol phosphate metabolism is blocked by low concentrations of the ion. The most persuasive element in this theory was that it explained why the brain is particularly sensitive to lithium: the supply of free inositol in the central nervous system is critically dependent on inositol phosphate catabolism (which is potently blocked by the ion) unlike the periphery, which has ready access to dietary inositol. Thus, the presumption was that after some time, and particularly in those regions of the brain that exhibit high activity (those that underlie the pathological condition?), lithium would trap much of the cellular inositol as inositol phosphates. The resulting inositol deficiency would, in turn, be reflected in a similar reduction in inositol-containing phospholipids; as a consequence, neurotransmitters that act through this signalling pathway would be unable to induce the formation of the inositol lipid-derived mediators, inositol 1,4,5-trisphosphate ($InsP_3$) and 1,2-diacylglycerol, that are essential for neurotransmission. The resultant inefficiency in neuronal communication would be particularly localized to areas of the brain that were highly active before drug treatment. If, as seems likely, the manic state results from this hyperactivity, an improvement in the clinical condition might then be expected to occur.

The data of Avissar *et al.* are important in that they suggest another potential biochemical end-point for the action of lithium that is affected by therapeutically relevant concentrations. They are preliminary, however, and further work is needed to establish whether this interaction can yield a preferential effect on the brain analogous to the clinical picture: all cells in the body exhibit G-protein-dependent phenomena and it is not immediately evident why, if the effect is present in lithium-treated manic patients, the function of peripheral tissues should not be affected.

In recent years, the ability of lithium to amplify inositol lipid-linked signalling by inhibiting inositol phosphate catabolism has been of enormous benefit in the detection of responses in tissues and cells that contain only a few receptors[6]. Direct effects of lithium on the levels of the important second-messenger molecules derived from the pathway are, however, only rarely seen[7] and, in these examples, the physiological consequence was unclear. The work of Irvine and his collaborators[8,9], some of which was reported in a recent issue of *Nature*, suggests that $InsP_4$ may be involved in the regulation of intracellular calcium homoeostasis by facilitating influx of the cation (see the News and Views article[10] by Jennifer Altman).

Unique action

Moreover, Batty and Nahorski[5] have recently demonstrated that the accumulation of $InsP_4$ is decreased by lithium in brain slices that have been stimulated by cholinergic agonists. Studies in peripheral tissues have, thus far, failed to reproduce this effect and, although the mechanism underlying it remains to be established, it is possible that the unique action of lithium on the central nervous system might be related to its ability to decrease $InsP_4$-dependent effects on calcium influx.

Attempts to extrapolate these lithium-sensitive biochemical events to the action of this ion in manic patients will be viewed, justifiably, with some caution by clinicians. It may be, in fact, that the most elegant proof that a relationship exists between the two phenomena will emerge if some of the current pharmaceutical industry interest in drugs targeted against inositol phosphate catabolism results in another active anti-manic drug. □

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Alan H. Drummond is at British Bio-technology Ltd, Watlington Road, Cowley, Oxford OX4 5LY, UK.

Corrigendum

In the obituary of John H. Northrop (*Nature* **329**, 396; 1987), the year that the Princeton branch of the Rockefeller Institute closed, and that Northrop moved to Berkeley, was 1949–50, not 1938–39 as stated. □