HOW DOES LITHIUM WORK ON MANIC DEPRESSION? Clinical and Psychological Correlates of the Inositol Theory

R. H. Belmaker, M.D., Yuly Bersudsky, M.D., Galila Agam, M.D., Joseph Levine, M.D., and Ora Kofman, M.D.

Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel

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ABSTRACT

How lithium works in manic-depressive illness is unknown. Recently, however, a powerful hypothesis has been gaining momentum. Distinguished by its testability and clinical implications, the inositol depletion hypothesis of lithium action is relevant to treatment of lithium side effects, to the development of new compounds with the clinical profile of lithium, and to new experimental treatment of depression.

LITHIUM

Lithium (Li) is a simple monovalent cation, which as a salt is used in the treatment of mania, in the augmentation treatment of depression, and in the prophylaxis of manic-depressive illness. As these are common disorders associated with almost normal life spans, large numbers of patients are being maintained on Li salt treatment. Lithium’s numerous clinical side effects, its interactions with antihypertensives and with general anesthesia, and its potential for neurotoxicity, however, make it a concern.

Li has numerous biological effects. It markedly increases choline levels in red blood cells, probably by inhibiting transport. However, the effect in red
blood cells is irreversible whereas the clinical effects of Li in manic depression disappear upon cessation of Li treatment. Li affects the enhanced binding of guanosine 5′-triphosphate to G-proteins caused by neurotransmitter stimulation of receptors. However, its ability to inhibit G-protein function is dependent on magnesium concentration and may not occur at physiological intracellular Mg²⁺ concentrations.

MOOD STABILIZERS

Since its discovery in 1949, Li’s effect on mania and depression, apparent opposite psychological states, and on other diverse cyclic psychological disorders such as cluster headache and premenstrual tension has remained unique. Recently, however, two anticonvulsants, carbamazepine and valproic acid, have been shown to be of prophylactic value in the treatment of manic depression. Though the clinical profiles of these two compounds overlap that of Li, they are not identical to it. Other anticonvulsants, such as phenytoin, are without effect in manic depression. No biological effect has been found that is unique to all three. This fact may preclude Li from the psychopharmacologic search for a common denominator in a family of drugs as has been found, for instance, with antischizophrenic drugs. All block dopamine receptors, which is strong evidence for the central role of dopamine blockade in the mechanism of action of antischizophrenic drugs. New compounds that block dopamine receptors are universally found to be antipsychotic. Similarly, all serotonin reuptake inhibitors are antidepressants and new serotonin reuptake inhibitors can be synthesized with considerable confidence about their clinical potential. As yet, however, the discovery of the new mood stabilizers has provided scant help in understanding the mechanism of action of Li.

INOSITOL

Inositol is a simple sugar-like compound present in the normal diet. By inhibiting inositol monophosphatase, the enzyme that synthesizes inositol in the brain, Li reduces brain inositol levels. The ability of Li to inhibit the enzyme is within the therapeutic range ($K_i = 0.86$ mM), and in vivo physiological effects of this inhibition are apparent in rats treated chronically with Li. The rats showed declines in brain inositol levels and a 20- to 40-fold buildup in the substrate, inositol monophosphate. Berridge et al (1) showed that several neurotransmitters cause breakdown of a membrane phospholipid, phosphatidylinositol-P2 (PIP2), into two second messengers, inositol triphosphate (IP3) and diacylglycerol (DAG). Describing the widespread role of the phosphatidylinositol (PI) cycle as a second messenger system, Berridge et al (1) noted the possible psychiatric implications of Li inhibition of inositol mono-
phosphatase. They suggested that Li inhibits PI-derived second messengers of activated systems only, without interfering with basal function. This hypothesis was based on the fact that inositol, derived from inositol phosphate breakdown, is essential for the resynthesis of PI. Overactive systems or overstimulated receptors would be dampened by Li’s depletion of the inositol pool available for resynthesis of the parent compound PI, whereas stable systems would be unaffected. This provides a possible explanation of Li’s paucity of effect in normal behavior and its powerful effects in mania and depression.

Based on Berridge’s theory, inositol reversal has been used by several groups as a technique to study the role of Li on the PI system (2). Because Li clearly has multiple biochemical effects, not all of which need be related to the therapeutic mechanism in mania and depression, it seemed critical to us to apply inositol reversal to behavioral effects of Li. However, inositol crosses the blood-brain barrier poorly. We thus compared intracerebroventricular (i.c.v.) injections of 10 mg of inositol in Li- and saline-treated rats. The rats were anesthetized with Nembutal® (50 mg/kg) and implanted with guide cannulae into the dorsal part of the third ventricle using standard stereotaxic procedures. Observed to behave normally with the chronic indwelling i.c.v. cannula, the rats were then injected intracranially with either 10 mg of myo-inositol or control solution.

Li-induced suppression of rearing is a well-described behavioral effect in rats. They received LiCl or NaCl intraperitoneally (i.p.) (5 meq/kg), and 24 hr later, after i.c.v. injection with inositol or vehicle, their activity was measured. Rats treated with Li showed less rearing than rats treated with saline. Administration of i.c.v. inositol reversed the Li effect. This was the first finding suggesting that inositol could reverse a behavioral effect of Li.

INOSITOL REVERSES Li-PILOCARPINE SEIZURES IN RATS

Although suppression of exploratory rearing in animals has some research value, this behavior has a large variance and is not always replicable. In order to study the dose-response relationship and the time-course of the behavioral effects of inositol on Li-treated rats, we sought a behavior that would give us a robust and consistent Li effect and that could then be modified by i.c.v. inositol. Therefore, we examined the effect of inositol on limbic seizures induced by Li-pilocarpine. Experiments on this model tested the ability of i.c.v. inositol to prevent Li-pilocarpine seizures. We first injected standard doses of Li (3 meq/kg) 24 hr prior to injection of pilocarpine (30 mg/kg). Twenty-eight male Sprague-Dawley rats were implanted with guide cannulae in the lateral ventricle, randomly divided into three groups, and 30 min prior to
treatment with pilocarpine injected i.c.v. with 10 mg of inositol (N = 10), control solution (N = 9), or the stereoisomer of inositol, 10 mg of L-chiro-inositol (N = 9), which is not known to possess biological activity.

The animals were rated for the progression of limbic seizures every 5 min for 75 min. The inositol-treated group had a significantly lower seizure score at 20 and 30–45 min. To determine if application of inositol could prevent, and not just delay, the occurrence of limbic seizures, we repeated the experiment using a lower dose of pilocarpine (20 mg/kg). Again, treatment with inositol significantly lowered the seizure score. Of 16 rats treated with inositol, 8 did not have limbic seizures at all, whereas only 1 of the 14 vehicle-treated rats did not exhibit clonus. All the rats treated with L-chiro-inositol had limbic seizures. Thus, in two experiments, inositol appeared to be a powerful and stereospecific antidote to the behavioral effects of Li.

Li TOXICITY AND LETHALITY

A major problem with Li treatment in humans is its narrow therapeutic window. Li toxicity involves the central nervous system, accompanied sometimes by seizures but always by sedation and coma. It would be of great theoretical importance, as well as great practical value, if inositol could reverse Li toxicity or lethality.

We attempted to prevent Li overdose death in rats with i.c.v. inositol. Twenty-eight male Sprague-Dawley rats weighing 300–400 g were implanted with guide cannulae in the lateral ventricle as described above. They were then injected i.c.v. with either control cerebrospinal fluid (CSF) solution, myo-inositol (10 mg), or L-chiro-inositol (10 mg), and then 90 min later with LiCl (14 meq i.p./kg). The inositol did not alleviate Li lethality, nor did it reverse inhibition of activity following toxic doses of Li (Table 1). Thus, Li toxicity and lethality apparently have a different biochemical basis from the behavioral and biochemical effects of Li described above, which is not surprising for an ion with so many biological effects.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Lack of effect of i.c.v. inositol on lethality following 14 meq of Li/kg(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>N</td>
</tr>
<tr>
<td>Vehicle</td>
<td>9</td>
</tr>
<tr>
<td>myo-Inositol</td>
<td>9</td>
</tr>
<tr>
<td>L-chiro-Inositol</td>
<td>10</td>
</tr>
</tbody>
</table>

*Modified from Reference 2.
DIFFICULTIES WITH THE INOSITOL THEORY OF Li ACTION

One problem with the inositol theory of Li action is that injection of 3 meq of LiCl/kg, a dosage leading to therapeutic plasma levels in humans, reduces rat brain inositol by less than 10%. It thus seemed important to study whether Li treatment in humans reduces CSF inositol levels. If inositol monophosphatase is the therapeutic site of Li action, measurement of the hypothesized CSF inositol–level reduction could predict response to Li in patients.

Li treatment was given to nine patients who agreed to participate in a trial of Li supplementation to ongoing therapy (3) at 1200 mg/day for 3–7 days. A lumbar puncture was performed on each patient by an experienced neurosurgeon on the morning before start of Li treatment and again 12 hr after the last dose. Li treatment did not reduce CSF inositol levels (25.7 ± 6.2 µg/ml before vs 27.7 ± 6.3 µg/ml after). Possibly that was the result because brain inositol levels are more than 10 times CSF inositol levels (4). With inositol concentrated so highly in the brain, lowering the concentrations might not be reflected in CSF levels. That more than one pool of brain inositol appears to exist may be another explanation. CSF inositol may equilibrate with the osmolyte-relevant brain pool and not with the neurochemically relevant PI cycle–related pool, which is more likely to be lowered by Li inhibition of inositol monophosphatase.

What might be the most serious problem in the inositol depletion hypothesis of Li action was suggested recently by Williams & Jope (5). They reported that epi-inositol, another biologically inactive isomer of myo-inositol, as well as myo-inositol itself, reverses Li-pilocarpine seizures. Following Jope, we gave seven rats i.c.v. myo-inositol, six rats control solution, and seven others epi-inositol i.c.v. (all 10 mg/40 µl) 90 min before injection with pilocarpine. None of the epi-inositol-treated rats seized, one of the myo-inositol-treated rats seized, and four of the control rats seized. The scientific meaning of an absence of effect of one stereoisomer, chiro-inositol, and a positive effect of two others, myo- and epi-inositol, is not clear. There is no evidence to suggest that epi-inositol epimerizes to myo-inositol in vivo. It is possible that epi-inositol can replace myo-inositol in osmolyte function and “push” myo-inositol into the pool for PI synthesis.

Based on existing evidence that inositol can reverse key behavioral effects of Li, it is reasonable to suggest that inositol monophosphatase inhibition might be the molecular therapeutic target of Li. If so, synthetic inositol monophosphatase inhibitors might be developed as a whole new class of psychoactive compounds with a clinical profile similar to that of Li. Efforts in this direction are already well under way (6).
THE EFFECT OF INOSITOL SUPPLEMENTATION ON Li-INDUCED POLYURIA-POLYDIPSIA

Rat Studies

Polyuria is a common side effect of Li treatment in humans. Li’s inhibition of antidiuretic hormone (ADH) function has classically been ascribed to its inhibition of ADH-sensitive adenylate cyclase (7). Recent research suggests crosstalk between the various second messenger systems, and it is possible that inositol depletion due to Li could affect the cyclic adenosine 5′-monophosphate response to ADH stimulation. To test whether inositol would mitigate Li-induced polydipsia-polyuria, 78 rats were given either 2.5% mannitol or 2.5% inositol mixed with regular tap water to drink (in addition to ad libitum food). Half the rats in each group were injected i.p. daily with 1.5 meq of LiCl and half were injected with NaCl/kg for 10 days, followed by 2.25 meq of LiCl or NaCl/kg, respectively, for 4 days. In addition to these four groups, a fifth group was injected with LiCl daily but drank tap water.

As expected, Li induced marked polydipsia starting from day 3 in rats drinking regular water, and from day 5 in rats drinking mannitol, compared to the groups treated with NaCl. Li-treated rats that drank the inositol solution developed significant polydipsia on days 13 and 14 only, at a much slower rate than rats drinking the mannitol solution or plain water. Li-treated rats that drank the inositol solution had significantly less polydipsia on days 2–6 than Li-treated rats that drank tap water. Thus, inositol markedly attenuated the development of polydipsia.

Patient Studies

To see if inositol would alleviate polyuria-polydipsia in patients treated with Li, 11 patients complaining of Li-induced polyuria-polydipsia were recruited for an open study approved by the Human Subjects Committee. Each patient was treated with 3 g of inositol daily (two capsules containing 500 mg of inositol three times daily) for 5 days. Complaints of polyuria and polydipsia were recorded daily by standard interview. The effects of inositol treatment on Li-induced polyuria-polydipsia are summarized in Table 2. Five of eleven patients reported a dramatic improvement of polyuria-polydipsia while another four showed mild improvement (8). Of course inositol is also an important kidney osmoregulatory substance (9) and its effects in Li-induced polyuria may be unrelated to its effects on second messengers. The study must be replicated in a controlled design. Other side effects of Li in these patients also improved on inositol treatment, and a recent semicontrolled case report of Li-induced psoriasis reported marked improvement after administration of inositol (10). Theoretically, the greatest danger in the use of inositol for the treatment of Li side effects might be the reappearance or exacerbation of
manic depression. This effect was not seen in the above study, perhaps because of the low dose of inositol used and the poor penetration of inositol into the brain.

THE PHARMACODYNAMICS OF INOSITOL EFFECTS

Inositol injected i.c.v. has a dramatic effect on limbic seizures, making it a useful paradigm in studying time-course and dose-response functions. We conducted a series of experiments in which we injected rats with 3 meq of LiCl/kg, as described above, and 10 mg of inositol i.c.v. at various time intervals (0, 1, 4, 8, 12, and 24 hr) prior to subcutaneous injection of pilocarpine. Inositol was effective at 1, 4, and 8 hr before administration of pilocarpine. When injected either immediately before or 24 hr before pilocarpine injection, inositol did not prevent seizures in any rat, and when injected 12 hr before, 50% of the rats seized. This time-course suggests that it is necessary for inositol to have time to distribute within the brain and enter cells, and that it is extruded from brain or metabolized within 8–24 hrs after injection (11).

To obtain a dose-response curve for inositol effects, 35 Li-treated rats were injected i.c.v. 1 hr prior to injection of pilocarpine either with control solution (N = 13) or with 5 (N = 16) or 10 (N = 6) mg of inositol. Prevention of seizures was significantly less with 5 mg of inositol i.c.v. than with the 10-mg dose. These data suggest a very steep dose-response curve for attenuation by inositol of the behavioral effects of Li. Normal brain concentrations of inositol are very high, about 10 mM (12), and the 10-mg dose is apparently necessary for optimal prevention of Li-pilocarpine seizures.

Table 2  The effect of inositol on Li-induced polyuria-polydipsia

<table>
<thead>
<tr>
<th>No</th>
<th>Age &amp; sex</th>
<th>Diagnosis</th>
<th>Li Level (mmol/l)</th>
<th>Polyuria-Polydipsia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>21, F</td>
<td>manic</td>
<td>0.8</td>
<td>1.18</td>
</tr>
<tr>
<td>2</td>
<td>38, F</td>
<td>manic</td>
<td>1.08</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>38, F</td>
<td>manic</td>
<td>1.1</td>
<td>1.12</td>
</tr>
<tr>
<td>4</td>
<td>47, M</td>
<td>manic</td>
<td>1.25</td>
<td>1.12</td>
</tr>
<tr>
<td>5</td>
<td>23, F</td>
<td>manic</td>
<td>0.85</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>32, F</td>
<td>manic</td>
<td>0.6</td>
<td>0.85</td>
</tr>
<tr>
<td>9</td>
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</tr>
<tr>
<td>10</td>
<td>35, F</td>
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<td>1.3</td>
</tr>
<tr>
<td>11</td>
<td>25, F</td>
<td>manic</td>
<td>0.71</td>
<td>0.82</td>
</tr>
<tr>
<td>12</td>
<td>68, F</td>
<td>depression</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>13</td>
<td>38, F</td>
<td>depression</td>
<td>0.85</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Modified from Reference 8. 0, None; +, mild; ++, moderate; ++++, severe.
CLINICAL TRIALS OF INOSITOL IN DEPRESSION

As with L-3,4-dihydroxyphenylalanine (DOPA), which enters the brain poorly but has proved in high doses to be effective in Parkinson’s Disease, we wondered if high-dose inositol could enter the brain and cause behavioral effects via neurotransmitter systems linked to PI as a second messenger. We injected male rats with LiCl i.p. (3 meq/kg), followed 18 hr later by 12 g of inositol i.p./kg (10% in isotonic saline) or an equal volume of glucose (13). Six hours after the peripheral inositol injection, rats were injected subcutaneously with pilocarpine and rated for limbic seizures as described above. Peripheral high doses of inositol significantly reduced Li-pilocarpine seizures. Cortical inositol levels were measured in rats treated with i.p. glucose or inositol. Inositol-treated rats had a 35% increase in cortical inositol.

In a human study, administration of 12 g of inositol daily was shown to raise CSF inositol levels by 70% (14). Inositol powder (6 g) dissolved in juice was given twice daily for 7 days. Lumbar punctures were performed between 8–10 A.M., in fasting subjects. The last dose of inositol was given at 8 P.M. on the evening before the second lumbar puncture. CSF samples were stored at −70°C. Free myo-inositol in CSF aliquots was analyzed as trimethylsilyl derivatives by gas-liquid chromatography (14). CSF inositol levels increased from a mean of 20.2 ± 6.3, to a mean of 34.6 ± 13, P = 0.011 (paired t-test). These data suggest that peripherally administered inositol at high enough doses can enter brain and affect behavior in rats (13) and can enter CSF in humans (14). The i.c.v. dose-response and time curves suggest that twice daily administration of inositol may be sufficient for behavioral effects but that the dose-response curve is steep, and thus the highest possible doses may be necessary to affect behavior.

Barkai et al (15) reported that CSF levels of inositol were lower in depressed patients than in normal subjects. In Europe, over-the-counter inositol has long been used as a folk remedy for anxiety and depression. We hypothesized that inositol may be deficient in the brains of some depressed patients. This does not contradict the concept that Li reduces inositol levels and that Li is an antidepressant, because the PI cycle serves as a second messenger for several balancing and mutually interactive neurotransmitters. Li could alleviate depression by reducing inositol and a primary hyperactivity of one hypothetical brain system; low inositol levels in another system could cause second-messenger dysfunction and thereby depression. Exogenous inositol could hypothetically alleviate inositol deficiency in one system without increasing inositol above normal levels in another.

After an encouraging open trial of 6 g of inositol administered daily for treatment-resistant depression (16), we performed a double-blind controlled trial in which 28 depressed patients were given 12 g of inositol daily for 4
weeks (17). Significant overall benefit from treatment with inositol compared to placebo was found at week 4 but not at week 2 on the Hamilton Depression Scale (HDS). Item analysis of the HDS found significant effects of inositol use compared with placebo on mood, insomnia, anxiety, agitation, diurnal variation, and hopelessness. No changes were noted in hematologic, renal, or liver function. A follow-up double-blind controlled trial of inositol treatment in panic disorders, a condition often responsive to antidepressants, revealed significant benefit from the inositol (18).

Inositol use has had no significant side effects in more than 100 patients who have participated in our studies in psychiatry (19). Moreover, high doses of inositol have been used with good results intravenously in the treatment of respiratory distress syndrome in neonates (20) and have been reported to have beneficial effects in diabetic neuropathy (21). In respiratory distress syndrome, it has been suggested that inositol treatment affects the synthesis rate of key surfactant phospholipid components. In diabetic neuropathy, it is hypothesized that elevated blood glucose prevents inositol uptake into nerves by competing at the inositol transporter, thus starving the neuron’s PI function in a manner that can be reversed by oral inositol supplementation. In psychiatry, the mechanism of inositol’s effects may be much more complex than that of the original concept of Li lowering of inositol levels and inositol reversal of Li effects to maintain PI supplies. Inositol has recently been shown to regulate the function of the PI cycle in a complex manner (22). Complex regulation of a cycle can lead to “pendulum” effects where a push from either direction causes an identical effect. Indeed, when inositol was administered after Li, it reversed the effects of Li on protein kinase C levels, whereas administration of inositol alone mimicked the effects of Li (23). This apparent paradox may hint at a solution to the mystery of how Li administration benefits both mania and depression.

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