Bipolar Disorders 2006: 8: 152–159

BIPOLAR DISORDERS

Original Article

Inositol deficiency diet and lithium effects

Shaldubina A, Stahl Z, Furszpan M, Regenold WT, Shapiro J, Belmaker RH, Bersudsky Y. Inositol deficiency diet and lithium effects. Bipolar Disord 2006: 8: 152–159. © Blackwell Munksgaard, 2006

Objectives: A major hypothesis explaining the therapeutic effect of lithium (Li) in mania is depletion of inositol via inhibition of inositol monophosphatase. However, inositol is also present in the diet. Restriction of dietary inositol could theoretically enhance the effects of Li.

Methods: We used dietary inositol restriction in animal studies and also devised a palatable diet for humans that is 90% free of inositol.

Results: Dietary inositol restriction significantly augmented the inositol-reducing effect of Li in rat frontal cortex. Li reduced inositol levels by 4.7%, inositol-deficient diet by 5.1%, and Li plus inositol-deficient diet by 10.8%. However, feeding with the inositol-deficient diet did not enhance the behavioral effect of Li in the Li-pilocarpine seizure model.

Fifteen patients participated in an open clinical study of the inositol-deficient diet: six rapid cycling bipolar patients responding inadequately to Li or valproate in different phases of illness; two Li-treated bipolar outpatients with residual symptomatology, and seven inpatient Li-treated bipolar patients in non-responding acute mania. The diet had a major effect in reducing the severity of affective disorder in 10 of the patients within the first 7–14 days of treatment.

Conclusion: These results suggest that dietary inositol restriction may be useful in some bipolar patients, but controlled replication is necessary.

Alona Shaldubina[a], Ziva Stahl[a], Mariala Furszpan[a], William T Regenold[b], Joseph Shapiro[a], Robert H Belmaker[a] and Yuly Bersudsky[a]

[a]Stanley Research Center, Ministry of Health, Beer-Sheba Mental Health Center, Beer-Sheva, Israel, [b]University of Maryland School of Medicine, Baltimore, MD, USA

Key words: behavior – inositol deficiency diet – Li–pilocarpine seizures – lithium – rats

Received 16 July 2004, revised and accepted for publication 10 November 2005

Corresponding author: Dr Yuly Bersudsky, Beer-Sheba Mental Health Center, PO Box 4600, Beer-Sheba, Israel. Fax: 9728-640162; e-mail:yuly@bgumail.bgu.ac.il

A major hypothesis explaining the therapeutic effect of lithium (Li) in mania is inhibition of inositol monophosphatase. This reduces levels of inositol, resulting in a decreased ability of neurons to generate the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG) and therefore to react to transmitters acting via the phosphoinositide second messenger system (1). The enzymatic degradation of inositol monophosphate (IP_1) to inositol is uncompetitively inhibited by Li in the range of therapeutic concentrations. IP_3 is degraded by inositol polyphosphate monophosphatase to inositol biphosphate (IP_2) and inositol monophosphate (IP_1), and from there by inositol monophosphatase to inositol (1). Subsequently, inositol combines with cytidine monophosphoryl-phosphatidic acid, a metabolite of DAG, to form phosphatidyl inositol (PI), from which PIP_2 can be resynthesized and thus made available for renewed production of IP_3 and DAG (2).

Inositol is present in the diet from both animal and plant sources which provide the average adult human with approximately 1 g of total inositol per day (3). Inositol is also formed from glucose (in such organs as testis, liver, kidney and brain) in amounts which together equal approximately 5 g per day (4). The synthesis of inositol from glucose occurs via inositol monophosphate, and therefore the inhibition by Li of inositol monophosphatase inhibits not only recycling of inositol phosphates but also impairs *de novo* synthesis of inositol from glucose. Only dietary inositol is not compromised by Li treatment.

We proposed that dietary inositol could be important in explaining variability and resistance to Li treatment in bipolar disorder (5). While

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

depletion of dietary inositol may have few physiologic effects when accomplished alone and inositol is not usually considered an essential nutrient (6), the combination of Li and dietary inositol restriction could have more marked clinical effects. Although inositol provided by diet may not be needed under normal conditions to replenish losses from the PI cycle, Li treatment that inhibits endogenous synthesis should increase the dependence on dietary inositol markedly. Agonist stimulation in the presence of Li can deplete a rat brain of up to 30% of its inositol (7), and thus a manic patient with speculatively hyperactive neurotransmission could require up to 4 gm of inositol per day to replace one third of the total inositol in a 1.2 kg human brain. Restriction of dietary inositol could markedly augment the effects of Li (8). Restriction of dietary inositol could also augment valproate treatment, since valproic acid reduces inositol synthesis in a manner similar to, but distinct from, Li (9–11). It is also possible that inositol depletion could exacerbate the side effects of Li, some of which may be due to the effects of Li on inositol metabolism (12, 13).

We report here on exploratory studies of inositol-deficient diet as an augmenting method for Li treatment of mania and bipolar disorder. First, we replicated our previous preliminary animal study (8) that indicated that dietary inositol restriction may have an effect on inositol level in the brain and enhance the effects of Li. Second, we evaluated possible behavioral effects of feeding with an inositol-deficient diet on the enhancement of pilocarpine seizures in rats treated with Li (14). Such seizures induced by Li and pilocarpine are stereospecifically reversible by intracerebroventricular inositol, and have been considered a behavioral effect of inositol depletion by Li (14). Third, we devised a palatable diet for humans that is 90% free of inositol and tested in a preliminary open study the hypothesis that such a diet would augment the clinical effect of Li and/or valproic acid.

Methods

Animals

Male Sprague–Dawley rats (starting weight 200–250 g) were randomly divided into treatment groups and housed in individual polycarbonate cages. All animals were exposed to a 12-h light/dark cycle and had free access to food and water. The regular food group was fed ordinary rat chow. The Li supplement in food was 0.2% LiCl supplement to ordinary chow. The inositol deficiency food group received only artificial food not containing inositol (sugar 65%, casein 25%, soya oil 5%, minerals 4%, and vitamins 1%).

Serum Li concentration was determined in carotid blood obtained at the time of decapitation. One milliliter of blood from decapitated control and Li-treated rats was centrifuged at 9000 *g* for 10 min. Serum Li levels were measured using an ion-selective electrode apparatus.

The study was approved by the Ben-Gurion University (Beer-Sheva, Israel) Institutional Review Committee for the Use of Animals, and the procedures were carried out in compliance with the Declaration of the National Institute of Health Guide for Care and Use of Laboratory Animals (15).

Analysis of brain inositol levels

After 11 days, rats were sacrificed by decapitation, and inositol levels were determined in replicate samples from cerebral cortex after storage at −70°C. Free *myo*-inositol was analyzed by gas chromatography (GC) using a capillary column as previously described (16) in half of the rat brains and half of the rat brains were sent to another laboratory (WTR) for replication by GC–mass spectrometry. Samples of tissue (approximately 50 mg) were dissected from the cerebral cortex, weighed, added to five volumes of distilled water containing a known amount of $(^2H)_6$ *myo*-inositol (Isotec, Inc., Miamisburg, OH, USA) internal standard, and homogenized. After adding two volumes of ice-cold absolute ethanol to precipitate protein, the solution was centrifuged at 3000 *g* for 30 min at 4°C, and the supernatant allowed to dry overnight using a Speed Vac Plus SC210A (Savant Instruments, Farmingdale, NY, USA). The dried residuum was then combined with 1 mL of ice-cold, distilled water, and centrifuged at 3000 rpm for 30 min at 4°C to precipitate remaining lipids. The supernatant was again dried overnight, and then combined with 100 μL of acetic anhydride in pyridine (2:1) for 20 min at 70°C to form hexaacetate derivatives. Inositol concentration was measured using the following previously reported gas chromatographic-mass spectrometric (GC-MS) method and an electron impact GC-MS system (Hewlett-Packard 5971B, Fullerton, CA, USA). One microliter of derivatized sample was automatically injected onto a 12 m × 0.20 mm HP-5MS column, with chromatographic conditions as follows: injector temperature 250°C; initial oven temperature 100°C, ramping to 215°C at 25°C/min, then to 270°C at 45°C/min; carrier gas (helium) flow rate 1.0 mL/min; and splitless

injection. Under these conditions, inositol eluted from the column at 9.3 min. The effluent from the GC column was directed into the MS source and subjected to electron impact ionization at 70 keV. Selected ion monitoring was performed at mass values 210 and 214, which were the values for the major peaks of the acetylated fragments of inositol and its deuterated, internal standard isotope, respectively. Endogenous inositol concentration was calculated from the peak area ratio (corrected for natural abundance) and the known amount of internal standard added. Samples were analyzed in duplicate, and the average coefficient of variation within sample runs was 3.7%.

Behavioral study

One group of animals (n = 10) received inositol deficiency food and a second (n = 10) regular food. All of them were treated with Li (0.2% in food for 17 days and 0.25% in food for last 8 days) before pilocarpine injection (10 mg/kg pilocarpine s.c.). After pilocarpine injection, the animals were placed in clear polycarbonate cages, and behavior scored by an observer who was blind to treatment condition.

Behavior was rated for signs of seizure according to a modified version of the scale used by Patel et al. (17): 0 – no response; 1 – gustatory movements and/or fictive scratching; 2 – tremor and/or hind limb extension; 3 – head bobbing; 4 – forelimb clonus; 5 – rearing, clonus, and falling. Each animal was observed for 15 s once every 5–10 min for 100 min. The latency to attain forelimb clonus (a score of 5) was recorded for each rat.

One hundred minutes after pilocarpine injection all animals were sacrificed by decapitation. Blood was collected from the cervical trunk for the determination of Li.

Clinical study

All patients who participated in the study had been treated previously in our bipolar clinic and had well documented histories of illness. Two experienced psychiatrists using an interview based on DSM-IV confirmed diagnosis. Patients participated in the open clinical trial if they met DSM-IV criteria for bipolar or schizoaffective disorder and had no serious physical illness including neurological illness or mental retardation. The study was approved by the Helsinki Committee and all patients gave written informed consent. Inclusion criteria for participating patients were: (i) rapid cycling bipolar patients who had responded inadequately to Li in either phase of illness; (ii) consenting Li-treated bipolar or schizoaffective outpatients with residual affective symptomatology; (iii) inpatient Li-treated bipolar or schizoaffective patients in non-responding acute mania. Patients with any active or serious physical illness were excluded and no patient had drug or alcohol abuse, or clinically significant Axis II disorder. Eleven patients were taking Li only as a mood stabilizer, three were taking Li plus valproate, and one patient on valproate alone was accepted after the results of O'Donnell et al. (9) and Shaltiel et al. (10). Patients were given usual treatment with typical or atypical neuroleptics in addition to the mood stabilizer.

All patients received dietary instruction to achieve inositol depletion (a palatable human diet with over 90% reduction of inositol content; 5, 18). Daily diet diaries were collected every week for the first month. Dietary supervision was available on a daily basis. The nutritional dietary compliance to the low inositol diet was evaluated using a Food Frequency Questionnaire adopted for this purpose. This scale allowed nutritional scoring and analysis of food consumption, a common method in nutritional studies (19). Inositol content in food was determined based on nutritional information (18). In the Food Frequency Questionnaire that we used the subjects were asked to describe the frequency of eating food containing high levels of inositol. Portion size was specified on the questionnaire. This information was used to calculate daily average inositol intake for that week. In addition, we also used the response to the Food Frequency Questionnaire to score the dietary compliance to the low inositol diet.

Clinical rating scales [Brief Psychiatric Rating Scale, Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAMD), and Clinical Global Impression] were administered by an experienced psychiatrist (MF) at baseline, weekly during the first month and monthly thereafter. Patients were dropped from the study in case of non-compliance to diet or severe exacerbation of symptoms that required changes in the pharmacological treatment. All patients were evaluated by the clinical treating physician at baseline, weekly during the first month and monthly thereafter for EKG, liver and kidney functions, and blood cell count. At each visit, treatment-emergent symptoms (side effects) were recorded on the Stanley Foundation Bipolar Network Appendix A form, and special attention was paid to common side effects of Li that could conceivably be exacerbated by inositol depletion.

Results

Animal

Inositol levels in the frontal cortex of rats treated with inositol deficiency diet. Table 1 shows the effects of inositol deficiency diet on frontal cortex inositol levels in rats treated with 0.2% Li chloride supplement in food for 11 days. One-way parametric ANOVA with planned comparison showed that inositol was significantly depleted by 10.8% only in Li plus inositol-deficient diet-treated group ($F = 4.1$, $df_{1,115}$, $p < 0.045$). In the Li-treated group and in the group which received inositol-deficient diet alone there was a trend (4.7% and 5.1%, respectively) toward inositol reduction.

Plasma Li levels in the Li-treated groups were not significantly different, and there was no correlation between Li levels in plasma and inositol levels in the frontal cortex ($p = 0.4$).

Lithium-pilocarpine seizures in rats fed an inositol-deficient diet. Table 2 illustrates the results. There was no difference in latency to clonus or number of animals attaining forelimb clonus between groups that received inositol deficiency diet or regular food.

Human

Fifteen patients participated in the open clinical study: six rapid cycling bipolar patients responding inadequately to Li or valproate in different phases of illness; two Li-treated bipolar outpatients with residual symptomatology; and seven inpatient Li-treated bipolar patients in non-responding acute mania.

Among the six rapid cycling patients only one was not compliant with diet and dropped out of the study. Another five responded to combination treatment within 2 weeks and maintained this improvement during combination treatment (9 ± 1.4 point improvement in YMRS for two patients with predominantly manic symptoms and 11 ± 5.7 in HAMD for three patients with predominantly depressive symptoms) (see Table 3). Among the seven Li-treated manic patients, two were not compliant with diet and did not respond. One who was compliant with diet did not improve during 2 weeks of treatment and stopped participation in the study. Another four Li-treated severe manic patients markedly improved within 1 week and became euthymic after 2 weeks (34.8 ± 9.7 point decrease in YMRS), and were still euthymic during the 4–5 months of continuation treatment. One of them was euthymic for 4 months and relapsed after cessation of diet (see Table 4). Of the two participating outpatients with residual symptoms, one bipolar woman with residual depression had little response over 2 months on the diet, and one 57-year-old woman with chronic hypomania resistant to Li over several years had marked response to the diet (6 point improvement in YMRS) within 1 month that was maintained for 5 months.

The diet had a major effect in reducing the severity of affective disorder in 10 of the 15 patients, including five of six rapid cycling bipolar patients (Table 3), four of seven non-responding acute manic patients (Table 4) and one of the two outpatients with residual symptoms as described above.

Table 1. Effect of inositol-deficient food (IDF) or regular food (RF) on frontal cortex inositol level

Treatment	n	Plasma lithium level (mmol/L; mean ± SE)	Frontal cortex inositol level (mmol/kg wet weight; mean ± SE)	% depletion
IDF + Li	31	0.95 ± 0.07	5.27 ± 0.17	10.8
RF + Li	33	1.05 ± 0.08	5.63 ± 0.26	4.7
IDF	26		5.61 ± 0.20	5.1
RF	29		5.91 ± 0.24	

One-way ANOVA; planned comparison show statistically significant differences only between RF versus IDF + Li groups ($F = 4.1$, $df_{1,115}$, $p < 0.05$).

Table 2. Effect of inositol-deficient food (IDF) or regular food (RF) on lithium–pilocarpine seizures in rats

Food	Protocol	Li plasma level (mmol/L; mean ± SD)	Pilocarpine s.c.	n	Seizure (%)	Time to seizures (min; mean ± SD)
IDF	0.2% LiCl in food for 17 days +	0.56 ± 0.1	10 mg/kg	10	90	34.6 ± 19.0
RF	0.25% LiCl in food for last 8 days	0.53 ± 0.04	10 mg/kg	10	90	34.1 ± 7.9

Table 3. Rapid cycling bipolar patients responding inadequately to lithium

		BPRS		YMRS		HAMD		CGI severity mania		CGI severity depre-ssion			
ID	Sex/age	B	End	B	End	B	End	B	End	B	End	Clinical background	Response
4	F/48	29	49	7	46	7	15	4	6	3	3	Rapid cycling, severe mania with 2 year hospitalization	Dropout (non-compliance)
7	M/52	29	20	0	0	15	6	1	1	4	1	Rapid cycling without euthymic intervals. Entered study after 2 months of treatment-resistant depression	Great improvement in depressive symptoms within 2 weeks. Has been stable and euthymic for 4 months
9	M/40	35	25	17	7	0	0	4	2	1	1	Rapid cycling without euthymic intervals, predominantly manic with long treatment-resistant hospitalizations. In moderate treatment resistant mania for 1 month on study initiation	Much improvement in manic symptoms within 1 week; maintained for 1 month; then dropped out of study
10	M/25	23	20	0	0	9	3	1	1	4	2	Rapid cycling without euthymic intervals. Entered study after 2 months of treatment-resistant depression	Great improvement in depressive symptoms within 2 weeks followed by 2 months of euthymia and depressive relapse[a]
14	M/59	26	18	8	0	0	0	3	1	1	1	Rapid cycling without euthymic intervals, predominantly manic. Entered study after 1 month of resistant mania	Much improvement in manic symptoms within 1 week. Complete euthymia for 2 months. Dropped from study with new angina pectoris
15	M/20	34	18	0	0	17	0	1	1	5	1	Rapid cycling without euthymic intervals. Entered study after 2 months of treatment-resistant depression	Much improvement in depressive symptoms within 2 weeks followed by 4 months euthymia

BPRS = Brief Psychiatric Rating Scale; YMRS = Young Mania Rating Scale; HAMD = Hamilton Depression Rating Scale; CGI = Clinical Global Impression; B = baseline.
[a]Data before exacerbation and poor compliance with diet.

Table 4. Lithium-treated bipolar patients in non-responding acute mania

		BPRS		YMRS		HAMD		CGI severity mania		CGI severity depression			
ID	Sex/age	B	End	B	End	B	End	B	End	B	End	Clinical background	Response
1	M/40	54	18	43	0	0	0	6	1	1	1	Severe manic episodes that never lasted <2 months despite intensive treatment. Entered study 2 weeks after onset of severe mania	Marked improvement after 1 week and euthymic by 2 weeks. Still euthymic after 5 months
3	F/42	34	20	23	2	6	1	5	1	1	1	Severe manic episodes, unstable remissions and long hospitalizations in the past. Entered study after 2 weeks of manic symptoms	Much improvement in manic symptoms within 1–2 weeks followed by 4 months of euthymia and manic exacerbation after cessation of diet[a]
6	F/43	57	22	48	8	3	1	6	2	1	1	Severe manic episodes, unstable remissions and long hospitalizations in the past. Entered study after 1 month of manic symptoms	Marked improvement in manic symptoms within 1–2 weeks followed by a month of euthymia. Stopped study to move to another city
8	M/27	39	41	23	19	0	0	5	5	1	1	Severe resistant mania after 3 months of hospitalization	No response to treatment; dropped out after 2 weeks
11	M/38	52	52	35	34	3	3	6	6	1	1	Mania severe, 5 month hospitalization, resistant to treatment	Non-compliance
12	M/25	45	45	23	23	0	0	6	6	1	1	Mania severe, 3 month hospitalization, resistant to treatment	Non-compliance
13	M/58	28	18	35	0	0	0	6	1	1	1	Long hospitalizations due to resistant-to-treatment manic episodes in the past, with short unstable remissions and hypomanic residual symptoms. Entered study following 1 month of severe manic symptoms	Much improvement in manic symptoms within 1 week and very much improvement within 2 weeks. Has been stable and euthymic for 4 months

BPRS = Brief Psychiatric Rating Scale; YMRS = Young Mania Rating Scale; HAMD = Hamilton Depression Rating Scale; CGI = Clinical Global Impression; B = baseline.
[a]Data before exacerbation and poor compliance with diet.

Three patients dropped out very early from the study because of non-compliance with the diet, and one because of non-response after 2 weeks. One patient was excluded from the study because of exacerbation of manic symptoms after 4 months of stable state. One patient was excluded from the study because of exacerbation of depressive symptoms after 2 months of stable state.

There was a slight elevation of subjective polydipsia in one case. One patient was excluded from the study after 4 months of stable state because of suspicion of a solitary mass in the neck. After workup, nothing pathological was found. One patient was excluded from the study after 2 months of stable state because of the onset of new unstable angina pectoris. There was no exacerbation of Li-induced EKG changes or of Li-induced leukocytosis.

Discussion

Dietary therapy is increasingly in use in the treatment and prevention of atherosclerosis, hypertension, colon cancer, and other diseases (20). In psychiatry dietary approaches became unpopular because of unsupported claims in the past. However, recent studies of omega-3 fatty acid treatment of affective disorder (21) and folic acid supplementation in schizophrenia (J. Levine, Z. Stahl, B.A. Sela, V. Ruderman, R.H. Belmaker, in press) emphasize the fact that metabolic intervention via diet may be important in the management of some psychiatric disorders.

We did not find a significant reduction of inositol levels in the frontal cortex of rats after inositol deficiency diet only or Li only. Because of *de novo* synthesis of inositol from glucose in the various tissues including the brain, dietary inositol restriction only was not expected to decrease inositol levels in the brain. Li treatment alone often has been reported to decrease inositol in the brain (9, 22), but these findings are not consistent (23) and the magnitude of the effect may vary with the brain area (hypothalamus more than frontal cortex) (24). Dietary inositol depletion together with Li treatment was hypothesized to reduce inositol levels more significantly than Li treatment alone, since only dietary inositol is available if inositol monophosphatase is inhibited by Li. This hypothesis was confirmed by direct inositol measurement in our study.

Lithium-pilocarpine seizures were not enhanced by inositol depletion. Li-pilocarpine seizures were reported to be reversed by *myo*-inositol and not by its biologically inactive stereoisomer *chiro*-inositol (25) and this constituted evidence that the model depended on inositol depletion. However, Bersudsky et al. (26) found that inositol depletion via hyponatremia did not result in Li-pilocarpine seizures. Moreover, Evans et al. (27) reported that Li enhances muscarinic excitation by presynaptic facilitation that is not related to inositol depletion (27). Thus the negative results of inositol depletion in this behavioral model do not strongly argue against the possible utility of inositol depletion to enhance the effects of Li in bipolar illness. The Li levels in the behavioral experiment (Table 2) were low because higher Li levels led to such rapid and powerful Li-pilocarpine seizures that a 'ceiling effect' could prevent inositol-deficient diet from having an effect. However, these lower levels might have allowed residual inositol synthesis from glucose and thus obviated any effect of the inositol-deficient diet. Either way, this behavioral model may have been inadequate to detect effects of the diet.

The diet had a major effect in reducing the severity of affective disorder in 10 of the patients within the first 7–14 days of treatment. Only two patients who were compliant with the diet did not respond, and another two who responded to treatment experienced exacerbation after cessation of diet.

No exacerbation of peripheral side effects of Li was seen, perhaps because the relatively lower demand of the PI cycle activity in the periphery affords some protection against the inositol-depleted diet aggravating Li-induced peripheral side effects. Such exacerbation could be a concern because inositol supplementation has been reported to ameliorate some side effects of Li such as polyuria (13) or psoriasis (12), and therefore augmented inositol depletion could conceivably bring out such side effects more severely than Li only.

The inositol depletion theory of Li action continues to generate interest and controversy. Williams et al. (28) recently reported a common effect of Li, carbamazepine and valproate on sensory neuron growth cones that was reversible with the addition of inositol. Similarly, Sarkar et al. (29) reported a common effect of Li, carbamazepine and valproate on a pathway regulating the half-life of cellular proteins that could be reversed with the addition of inositol. Silverstone et al. (30) reviewed human imaging findings supporting the inositol depletion hypotheses. However, A. Shaldubina, G. Agam, R.H. Belmaker, G. Berry and Y. Bersudsky (in prep.) studied sodium *myo*-inositol transporter heterozygous knockout mice. While showing 15% reduction in brain inositol, these animals did not show Li-like behavioral effects in the Porsolt swim

test. Perhaps a higher degree of inositol depletion is required for these behavioral effects.

Our clinical results are preliminary and need to be viewed with caution. The purpose of such an early study is to rule out the possibility of severe side effects, psychiatric or physical, and to judge acceptability of the intervention. Both objectives were achieved, and dietary inositol depletion can be said to be free of severe or common side effects in Li-treated patients and to be acceptable and practical for a significant number of patients. A controlled study is in order. While some might argue that a study of inositol supplementation to reverse the effects of Li and cause exacerbation of mania would be a more direct test of the inositol depletion hypothesis, an inositol deficiency diet is ethically more acceptable and also raises the possibility of a new practical treatment method.

Acknowledgement

Supported by a grant from the Stanley Medical Research Institute to YB.

References

1. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. Cell 1989; 59: 411–419.
2. Hertz L, Wolfson M, Hertz E, Agam G, Richards M, Belmaker RH. Lithium–inositol interactions: synthesis, uptake, turnover. In: Honig A, Ansseau M, van Praag HM, eds. Depression: Neurobiological, Psychopathological and Therapeutic Advances. England: John Wiley & Sons Ltd, 1997: 519–534.
3. Holub BJ. Metabolism and function of *myo*-inositol and inositol phospholipids. Annu Rev Nutr 1986; 6: 563–597.
4. Sherman WR. Lithium and the phosphoinositide signalling system. In: Birch NJ, ed. Lithium and the Cell. London: Academic Press, 1991: 121–157.
5. Bersudsky Y, Einat H, Stahl Z, Belmaker RH. *Epi*-inositol and inositol depletion: two new treatment approaches in affective disorder. Curr Psychiatry Rep 1999; 1: 141–147.
6. Aukema HM, Holub BJ. Inositol. In: Shils EO, Shike M, eds. Modern Nutrition in Health and Disease. Philadelphia, PA: Lea & Febiger, 1994: 466–473.
7. Honchar MP, Vogler GP, Gish BG, Sherman WR. Evidence that phosphoinositide metabolism in rat cerebral cortex stimulated by pilocarpine, physostigmine, and pargyline in vivo is not changed by chronic lithium treatment. J Neurochem 1990; 55: 1521–1525.
8. Bersudsky Y, Ziva S, Belmaker RH. Inositol depletion diet for augmentation of Li treatment. In: 39th Meeting of the American College of Neuropsychopharmacology, Puerto Rico, 2000 Conference Proceedings 369.
9. O'Donnell T, Rotzinger S, Nakashima TT, Hanstock CC, Ulrich M, Silverstone PH. Chronic lithium and sodium valproate both decrease the concentration of *myo*-inositol and increase the concentration of inositol monophosphates in rat brain. Brain Res 2000; 880: 84–91.
10. Shaltiel G, Shamir A, Shapiro J et al. Valproate decreases inositol biosynthesis. Biol Psychiatry 2004; 56: 868–874.
11. Vaden DL, Ding D, Peterson B, Greenberg ML. Lithium and valproate decrease inositol mass and increase expression of the yeast INO1 and INO2 genes for inositol biosynthesis. J Biol Chem 2001; 276: 15466–15471.
12. Allan SJ, Kavanagh GM, Herd RM, Savin JA. The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial. Br J Dermatol 2004; 150: 966–969.
13. Bersudsky Y, Vinnitsky I, Grisaru N et al. The effect of inositol on lithium-induced polyuria-polydipsia in rats and humans. Hum Psychopharmacol 1992; 7: 403–407.
14. Kofman O, Belmaker RH. Ziskind-Somerfeld Research Award 1993. Biochemical, behavioral, and clinical studies of the role of inositol in lithium treatment and depression. Biol Psychiatry 1993; 34: 839–852.
15. National Research Council. Guide for the Care and Use of Laboratory Animals. Washington, D.C.: National Research Council, National Academy Press, 1996.
16. Shapiro J, Belmaker RH, Biegon A, Seker A, Agam G. *Scyllo*-inositol in post-mortem brain of bipolar, unipolar and schizophrenic patients. J Neural Transm 2000; 107: 603–607.
17. Patel S, Meldrum BS, Fine A. Susceptibility to pilocarpine-induced seizures in rats increases with age. Behav Brain Res 1988; 31: 165–167.
18. Clements RS Jr, Darnell B. *Myo*-inositol content of common foods: development of a high-*myo*-inositol diet. Am J Clin Nutr 1980; 33: 1954–1967.
19. Willett W. Nutritional Epidemiology, Chapter 5. New York: Oxford University Press, 1998.
20. Wu L, Ashraf MH, Facci M et al. Dietary approach to attenuate oxidative stress, hypertension, and inflammation in the cardiovascular system. Proc Natl Acad Sci U S A 2004; 101: 7094–7099.
21. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002; 159: 477–479.
22. Allison JH, Blisner ME, Holland WM, Hipps PP, Shirman WB. Increased brain *myo*-inositol 1-phosphate in lithium-treated rats. Biochem Biophys Res Commun 1976; 71: 664–670.
23. Jope RS, Williams MB. Lithium and brain signal transduction systems. Biochem Pharmacol 1994; 47: 429–441.
24. Lubrich B, Patishi Y, Kofman O et al. Lithium-induced inositol depletion in rat brain after chronic treatment is restricted to the hypothalamus. Mol Psychiatry 1997; 2: 407–412.
25. Kofman O, Belmaker RH. Biochemical, behavioral, and clinical studies of the role of inositol in lithium treatment and depression. Biol Psychiatry 1993; 34: 839–852.
26. Bersudsky Y, Kaplan Z, Shapiro Y, Agam G, Kofman O, Belmaker RH. Behavioral evidence for the existence of two pools of cellular inositol. Eur Neuropsychopharmacol 1994; 4: 463–467.
27. Evans MS, Zorumski CF, Clifford DB. Lithium enhances neuronal muscarinic excitation by presynaptic facilitation. Neuroscience 1990; 38: 457–468.
28. Williams RS, Cheng L, Mudge AW, Harwood AJ. A common mechanism of action for three mood-stabilizing drugs. Nature 2002; 417: 292–295.
29. Sarkar S, Floto RA, Berger Z et al. Lithium induces autophagy by inhibiting inositol monophosphatase. J Cell Biol 2005; 170: 1101–1111.
30. Silverstone PH, McGrath BM, Kim H. Bipolar disorder and *myo*-inositol: a review of the magnetic resonance spectroscopy findings. Bipolar Disord 2005; 7: 1–10.