Lithium and Valproate Decrease Inositol Mass and Increase Expression of the Yeast INO1 and INO2 Genes for Inositol Biosynthesis*

Deirdre L. Vaden‡, Daobin Ding‡, Brian Peterson, and Miriam L. Greenberg§

From the Department of Biological Sciences, Wayne State University, Detroit, Michigan 48202

Bipolar affective disorder (manic-depressive illness) is a chronic, severe, debilitating illness affecting 1–2% of the population. The Food and Drug Administration-approved drugs lithium and valproate are not completely effective in the treatment of this disorder, and the mechanisms underlying their therapeutic effects have not been established. We are employing genetic and molecular approaches to identify common targets of lithium and valproate in the yeast Saccharomyces cerevisiae. We show that both drugs affect molecular targets in the inositol metabolic pathway. Lithium and valproate cause a decrease in intracellular myo-inositol mass and an increase in expression of both a structural (INO1) and a regulatory (INO2) gene required for inositol biosynthesis. The op1 mutant, which exhibits constitutive expression of INO1, is more resistant to inhibition of growth by lithium but not by valproate, suggesting that valproate may inhibit the Ino1p-catalyzed synthesis of inositol 1-phosphate. Consistent with this possibility, growth in valproate leads to decreased synthesis of inositol monophosphate. Thus, both lithium and valproate perturb regulation of the inositol biosynthetic pathway, albeit via different mechanisms. This is the first demonstration of increased expression of genes in the inositol biosynthetic pathway by both lithium and valproate. Because inositol is a key regulator of many cellular processes, the effects of lithium and valproate on inositol synthesis have far-reaching implications for predicting genetic determinants of responsiveness and resistance to these agents.

Bipolar disorder, or manic-depressive illness, is a common condition with a lifetime prevalence of 1–2% (1). It is characterized by recurring bouts of mania and depression, which have deleterious effects on career and interpersonal relationships. Approximately 15% of those afflicted commit suicide, and mortality rates because of physical disorders are also increased (2, 3). For decades, lithium has been the most effective agent for the treatment of bipolar illness (4). Despite the marked benefit that many patients obtain from lithium therapy, 20–40% of patients fail to show a satisfactory antimanic response to lithium, and many patients suffer significant morbidity (5). More recently, the branched fatty acid valproate has been used for treatment of bipolar disorder (6). Like lithium, it is not completely effective, and the molecular mechanisms underlying its therapeutic effects have not been elucidated. Lithium and valproate exert a variety of biochemical effects, only some of which are likely to be related to their therapeutic mechanisms of action. Identifying common targets of lithium and valproate is an approach that may more directly address the therapeutic mechanisms underlying their efficacy (7–11).

The inositol depletion hypothesis proposes that lithium acts by depletion of inositol from the brain. This is based on the observed uncompetitive inhibition of inositol monophosphatasess by lithium, resulting in decreased inositol, an increase in inositol phosphates, and subsequent down-regulation of the phosphoinositide cycle (12). Because the brain obtains inositol primarily from phosphoinositide turnover and de novo synthesis, it is highly sensitive to perturbations of the phosphoinositide cycle. Although there is considerable evidence that lithium affects the phosphoinositide second messenger system (13–15), a connection between this effect and the therapeutic mechanism of lithium has not been established. If inositol depletion formed the basis for the therapeutic effect, then valproate might be expected to deplete inositol, as well. Previous studies indicated that valproate does not inhibit bovine brain (16) or yeast inositol monophosphatase activity (17) and has a minimal effect on receptor-mediated phosphoinositide turnover (18). In addition, valproate does not lead to large accumulations of inositol mono- or bisphosphates, as seen with lithium (19).

We wished to determine whether valproate and lithium affect similar targets in the inositol metabolic pathway. The yeast Saccharomyces cerevisiae is an excellent model in which to address this question. Many of the genes that encode components of the phosphoinositide pathway have been cloned in yeast, and regulation of inositol metabolism in yeast is understood at a molecular level (20, 21). Expression of the structural gene INO1, coding for Ins-1-P1 synthase, is repressed in the presence of inositol. The products of the positive transcriptional regulators INO2 and INO4 form a heterodimer that leads to derepressed expression of INO1 in the absence of inositol. The negative regulator Op1p is required for repression of INO1 in the presence of inositol, and defects in this gene result in constitutive expression of INO1 and an inositol excretion phenotype. The regulatory gene INO2 is controlled in a similar manner, i.e. its expression is increased in the absence and repressed in the presence of inositol. Inositol is a key metabolic sensor, and inositol levels play a major role not only in regulating inositol biosynthesis but also in regulation of phospholipid biosynthesis and the glucose and unfolded protein response pathways (21).

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‡ Contributed equally to this work.
§ To whom correspondence should be addressed. Tel.: 313-577-5202; Fax: 313-577-6891; E mail: MLGREEN@sun.science.wayne.edu.

1 The abbreviations used are: Ins-1-P, inositol 1-phosphate; TEAB, triethylammonium bicarbonate.
Because conservation of function has been demonstrated from yeast to humans, an understanding of the molecular targets of lithium and valproate in yeast may have far-reaching implications for understanding the mechanisms of action of these drugs. In this study, we demonstrated that both lithium and valproate affect common targets in the inositol metabolic pathway and deplete inositol by different mechanisms.

**MATERIALS AND METHODS**

**Yeast Strains, Media, and Reagents**—The *S. cerevisiae* strains used in this study included SMY15 (derivative of D273-10B/A1, met6, ura3-52, MATa), SH302 (derivative of PMY168, his3∆200, leu2Δ1, trp1Δ63, ura3–52), and SH304 (same as SH302 except opil1::LEU2). Minimal synthetic defined medium contained glucose (2% w/v), necessary amino acids (histidine; 10 mg/l), leucine (60 mg/l), methionine (10 mg/l), tryptophan (10 mg/l), and uracil (10 mg/ml), and the salts and vitamin components of Difco Vitamin Free Yeast Base. Complex medium (YPD) contained glucose (2% w/v), bacto-peptone (2% w/v), agarose (2% w/v), and yeast extract (1% w/v).

DEAE dextran, NAD, myo-inositol dehydrogenase, myo-inositol, myo-inositol monophosphate, resazurin, TEAB buffer, and valproic acid were purchased from Sigma. Alkaline phosphatase and hexokinase were purchased from Roche Molecular Biochemicals. AG1-X8 (200–400 mesh size) were purchased from Bio-Rad. Sep-Pak Accell Plus QMA cartridges were from Waters Corp. (Milford, MA). Lithium chloride was obtained from Fisher.

**Growth of Yeast Cells**—Liquid cultures supplemented with the indicated concentrations of lithium, valproate, or inositol were inoculated to an A550 of 0.07. To determine lithium sensitivity on plates, cells from an overnight culture were washed four times in water, cell number was determined by microscopic counting using a hemocytometer, and the desired number of cells were spotted on plates containing the drugs. All growth was monitored at 30 °C.

**Measurement of Intracellular Lithium**—Cells were grown to stationary phase in minimal synthetic medium in the presence of the indicated concentrations of lithium. Cells were centrifuged at 4 °C for 5 min and washed twice in osmotic buffer (20 mM magnesium and appropriate sorbitol to achieve the same osmolarity as media containing lithium). Cells were disrupted, and cytosolic and vacuolar compartments were obtained by differential centrifugation (22). Intracellular lithium was determined by atomic absorption spectrophotometry and calculated by the method of Welihinda et al. (23).

**Measurement of Intracellular Inositol and Inositol Monophosphate**—Cells were grown in minimal synthetic medium at 30 °C in the presence or absence of lithium or valproate. Aliquots were harvested by centrifugation. Cells were washed three times and resuspended in water (~1 mg/l cells), and glass beads were added to ~50% of the volume of the suspension. Each sample was vortexed for 10 min at 2-min intervals, alternating with 2-min incubations on ice. The cell extracts were clarified by centrifugation for 2 min at 2,000 × g, and the supernatants were transferred to Eppendorf tubes and centrifuged for 15 min at 14,000 × g. The supernatants were collected and frozen at ~80 °C. The protein was quantified by the Bradford assay with bovine serum albumin as a standard (24). Intracellular inositol mass per 100 μg of protein was determined by the enzyme-coupled fluorescent assay of Maslanski et al. (25). To measure inositol monophosphate (per 1–4 mg of protein), cell extracts were prepared as described above. Inositol and inositol phosphates were resolved by Sep-Pak Accell Plus QMA cartridges, utilizing an Amersham Pharmacia Biotech variable flow pump. The cartridges were washed two times in osmotic buffer (20 mM magnesium and appropriate sorbitol), and inositol monophosphate was eluted in 10 ml of H2O followed by 4 ml of 1.2 mM lithium and 0.6 mM valproate. Because yeast is a free-living unicellular organism, it is susceptible to toxic concentrations of deleterious cations in the environment. Yeast cells possess two mechanisms to counteract lithium toxicity, exclusion of lithium from the cell (28), and compartmentalization of lithium within the vacuole where it is unable to affect cell functions (29). As a result of differences in these mechanisms, yeast strains differ widely in their degrees of sensitivity to lithium. In two wild type strains used in this study, SH302 and SMY15 were grown in inositol-free medium containing the indicated extracellular concentration of lithium or valproate (VPA) for 24 h. Cell extracts were prepared, and the concentrations of myo-inositol per 100 μg of protein were determined by the method of Maslanski and Bussa (25) as described under “Materials and Methods.”

**RESULTS**

**Intracellular Concentration of Lithium**—We wished to determine the effects of lithium and valproate in concentrations that were within the therapeutic range achieved in patients (0.6–1.2 mM lithium and 0.6 mM valproate). Because yeast is a free-living unicellular organism, it is susceptible to toxic concentrations of deleterious cations in the environment. Yeast cells possess two mechanisms to counteract lithium toxicity, exclusion of lithium from the cell (28), and compartmentalization of lithium within the vacuole where it is unable to affect cell functions (29). As a result of differences in these mechanisms, yeast strains differ widely in their degrees of sensitivity to lithium. In two wild type strains used in this study, SH302 and SMY15, 7.5 mM extracellular lithium led to a cytosolic concentration of less than 1 mM (Fig. 1). Although cytosolic and vacuolar lithium concentrations increased with increased extracellular lithium, the majority of lithium internalized was sequestered to the vacuoles. In 100 mM extracellular lithium, the cytoplasmic concentration in SMY15 was still only 2.6 mM, whereas the cytoplasmic lithium in SH302 was almost 10 mM.

In contrast to lithium, there is no evidence to suggest that valproate uptake is different in yeast and mammalian cells.

**Fig. 1. Intracellular lithium in *S. cerevisiae*.** Wild type strains SH302 and SMY15 were grown in inositol-free medium containing the indicated extracellular concentration of lithium for 24 h. Cell extracts were prepared, and the concentrations of lithium in cytosolic and vacuolar compartments were determined as described under “Materials and Methods.”

**Fig. 2. The effects of lithium and valproate on intracellular inositol mass.** Wild type strains SH302 and SMY15 were grown in inositol-free medium containing the indicated extracellular concentration of lithium or valproate (VPA) for 24 h. Cell extracts were prepared, and the concentrations of inositol per 100 μg of protein were determined by the method of Maslanski and Bussa (25) as described under “Materials and Methods.”
Indeed, the effects we observed with this drug on intracellular inositol and expression of INO1 and INO2 were apparent with 0.6 mM valproate, the therapeutic dose, as discussed below.

Growth in lithium or valproate leads to decreased intracellular inositol mass. Growth in the presence of lithium for several generations led to a decrease in inositol mass in both SH302 and SMY15 (Fig. 2). A greater decrease in response to increasing lithium was observed in SH302 than in SMY15. This may reflect the greater cytoplasmic lithium concentration in SH302 (Fig. 1). Although steady-state intracellular inositol did not appear to decrease greatly in SMY15, this strain exhibited a transient decrease in inositol mass, even in response to low concentrations of lithium. As seen in Fig. 3, the addition of 15 mM (extracellular) lithium to mid-log phase cells resulted in a 24% decrease in inositol mass by 6 h. At this time, intracellular inositol levels began to increase until wild type levels were restored (within 24 h). A decrease in inositol mass was also seen during growth in the presence of valproate (Fig. 2). In contrast to the effects of lithium, the valproate-induced decrease in inositol was not significantly different in the two strains. These data indicate that both lithium and valproate cause decreased intracellular inositol.

**Expression of INO1 and INO2 Is Increased during Growth in Lithium or Valproate**—Transcription of the structural gene INO1, as well as the positive transcriptional regulator INO2, is increased when inositol is limiting (20). Therefore, agents that cause a decrease in intracellular inositol would be expected to increase expression of these genes. The effects of lithium and valproate on expression of INO1 and INO2 were analyzed in Northern blots. As shown in Fig. 4, INO1 expression in SH302 is increased 5.6- and 13.5-fold in the presence of 7.5 and 15 mM lithium, respectively (Fig. 4A). The increased expression of INO1 is attenuated during growth in the presence of inositol (Fig. 4C). Thus, cells grown in 40 
μM inositol show only very slightly increased INO1 expression in 7.5 mM lithium and less than a 6-fold increase in expression in 15 mM lithium.

Growth in the presence of 0.1 and 0.6 mM valproate in the absence of inositol resulted in a 5.2- and 34.7-fold increase in INO1 mRNA, respectively (Fig. 5A). In the presence of 40 
μM inositol, even 0.6 mM valproate did not cause an increase in INO1.

Expression of INO2 in cells grown without inositol is about twice as high as in cells grown in 75 
μM inositol (see Fig. 4, B and D and Fig. 5D). Growth in 7.5 mM lithium caused a 2.4-fold increase in INO2 expression (Fig. 4B). Similarly, valproate caused a 1.5- to 2.5-fold increase in INO2 expression (Fig. 5). INO1 expression in SMY15 is also increased in response to lithium and valproate, although to a lesser extent than in SH302 (data not shown). In summary, lithium and valproate cause an increase in expression of both INO1 and INO2, genes...
that are derepressed in response to decreased intracellular inositol.

The opi1 Null Mutant Exhibits Increased Intracellular Inositol and Increased Resistance to Lithium but Not Valproate—Opi1p is a negative regulator that represses transcription of INO1 in the presence of inositol (20). Opi1 mutant cells express INO1 constitutively, leading to increased Ins-1-P synthase and the inositol excretion phenotype (30). We observed that the opi1 null mutant has dramatically increased levels of intracellular inositol (Fig. 6A). To determine whether the opi1 mutant has altered sensitivity to lithium or valproate, equal amounts of mutant and isogenic wild type cells were seeded on plates containing high concentrations of drug. Interestingly, growth of the opi1 mutant was less sensitive to lithium (Fig. 6B) but did not show altered sensitivity to valproate (data not shown).

Inositol Monophosphate Levels Are Decreased during Growth in Valproate and Increased during Growth in Lithium—The inability of the opi1 mutant to overcome valproate inhibition despite higher levels of Ins-1-P synthase suggested that this reaction might be inhibited by valproate. Inhibition of this reaction by valproate would lead to decreased levels of Ins-1-P. Therefore, inositol monophosphate levels were measured in wild type and opi1 mutant cells grown in the presence or absence of valproate. As seen in Fig. 7, inositol monophosphate levels in the wild type strain grown in 0.6 and 2.5 mM valproate were reduced to 30 and 16%, respectively, of the control (growth in the absence of drug). Levels of inositol monophosphate in the opi1 mutant were about 10-fold higher than in the wild type (consistent with the 10-fold increase in intracellular inositol observed in the mutant; see Fig. 6). As observed with wild type cells, growth of mutant cells in the presence of valproate also resulted in a decrease in inositol monophosphate.

Because lithium inhibits the inositol monophosphatase, inositol monophosphate levels are expected to increase during growth in the presence of lithium. Fig. 8 depicts inositol monophosphate levels in extracts of cells grown in the presence of lithium. In extracts of lithium-grown cells of both wild type and opi1 mutant, inositol monophosphate was increased.

DISCUSSION

In this report, we show that both lithium and valproate have a profound effect on inositol metabolism in the eukaryote S. cerevisiae. Both drugs, in therapeutically relevant concentrations, cause a decrease in intracellular inositol mass and an increase in expression of a structural (INO1) and a regulatory (INO2) gene required for inositol synthesis. The mechanism of inositol depletion by lithium is most likely by inhibition of inositol monophosphatase, as previous studies have shown that lithium inhibits yeast inositol monophosphatase activity and reduces expression of the INM1 gene (17, 31). We propose that the mechanism of inositol depletion by valproate is most likely via inhibition of Ins-1-P synthase.

Because yeast strains vary widely in their sensitivities to cations (32), we measured cytosolic lithium and intracellular inositol levels in two different wild type strains, SH302 and SMY15, SH302, which had higher cytosolic lithium than SMY15 (Fig. 1), exhibited a more pronounced decrease in intracellular inositol (Fig. 2). Lithium caused increased expres-
The op1 mutant has increased intracellular inositol and increased resistance to lithium. A, cells from op1 mutant and isogenic wild type (WT) strains were grown in synthetic inositol-free medium for 24 h. Intracellular inositol was determined as described in the legend to Fig. 2. B, equal amounts of op1 mutant and isogenic wild type cells were spotted on plates containing 0–600 mM lithium. Plates were incubated at 30 °C for 5–6 days.

Wild type (WT) and op1 mutant cells were grown in synthetic inositol-free medium in the presence of the indicated concentrations of valproate ([VPA]). Cell extracts were prepared, and inositol monophosphate levels were measured per 2 mg of protein by the method of Maslanski and Busa (25) as described under “Materials and Methods.”

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In summary, we have shown that therapeutically relevant concentrations of both lithium and valproate cause inositol depletion and affect expression of structural and regulatory genes in the inositol biosynthetic pathway. The increase in INO2 is especially significant, because this transcriptional activator regulates expression of more than 20 genes, in addition to INO1 (20). These include genes for phospholipid synthesis, as well as genes with no direct link to lipid synthesis. In addition to its role in phosphoinositide signaling, inositol is a key metabolic sensor involved in the regulation of numerous

3 S. Ju and M. L. Greenberg, unpublished data.

2 D. Ding, unpublished observations.

How do lithium and valproate decrease intracellular inositol? A likely mechanism for the lithium-induced decrease is via inhibition of inositol monophosphatase activity (17, 31, 34). We propose that valproate leads to decreased inositol by inhibition of the Ins-1-P synthase reaction. The experiments depicted in Figs. 7 and 8 demonstrate that inositol monophosphate levels are reduced by valproate but not by lithium. Inhibition of this reaction by valproate is further supported by the observation that the op1 mutant does not exhibit increased resistance to valproate, despite constitutive expression of INO1 and increased levels of Ins-1-P synthase (30). Previous findings that valproate does not inhibit inositol monophosphatase or cause an accumulation of inositol phosphates (16, 19) have been cited as evidence against the inositol-depletion hypothesis. The experiments shown in this report indicate that valproate does indeed cause inositol depletion. However, the mechanism of inositol depletion by valproate is not by inhibition of inositol monophosphatase but most likely by inhibition of the rate-limiting step in the de novo synthesis of inositol, i.e. the synthesis of Ins-1-P.

We speculate that, in addition to inhibition of de novo synthesis of Ins-1-P, another possible mechanism for the valproate-induced decrease in inositol is by down-regulating expression or activity of protein kinase C. Although there is no evidence for this in yeast, valproate does decrease mammalian protein kinase C expression (8). Protein kinase C appears to be required for inositol synthesis, as yeast protein kinase C mutants are inositol auxotrophs.3 Therefore, a valproate-mediated decrease in protein kinase C would result in decreased intracellular inositol, reduced expression of INM1 (which is down-regulated at low inositol levels) (17), and thus a further reduction in synthesis of inositol.

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In summary, we have shown that therapeutically relevant concentrations of both lithium and valproate cause inositol depletion and affect expression of structural and regulatory genes in the inositol biosynthetic pathway. The increase in INO2 is especially significant, because this transcriptional activator regulates expression of more than 20 genes, in addition to INO1 (20). These include genes for phospholipid synthesis, as well as genes with no direct link to lipid synthesis. In addition to its role in phosphoinositide signaling, inositol is a key metabolic sensor involved in the regulation of numerous.

FIG. 6. The op1 mutant has increased intracellular inositol and increased resistance to lithium. A, cells from op1 mutant and isogenic wild type (WT) strains were grown in synthetic inositol-free medium for 24 h. Intracellular inositol was determined as described in the legend to Fig. 2. B, equal amounts of op1 mutant and isogenic wild type cells were spotted on plates containing 0–600 mM lithium. Plates were incubated at 30 °C for 5–6 days.

FIG. 7. Valproate causes a decrease in inositol monophosphate. Wild type (WT) and op1 mutant cells were grown in synthetic inositol-free medium in the presence of the indicated concentrations of valproate ([VPA]). Cell extracts were prepared, and inositol monophosphate levels were measured per 2 mg of protein by the method of Maslanski and Busa (25) as described under “Materials and Methods.”

FIG. 8. Lithium causes an increase in inositol monophosphate. Wild type (WT) and op1 mutant cells were grown in synthetic inositol-free medium in the presence of the indicated concentrations of lithium. Inositol monophosphate levels were measured per 2 mg of protein.
cellular processes including phospholipid metabolism, the unfolded protein response, and the glucose response (21). Therefore, perturbation of inositol metabolism by these drugs will no doubt have far-reaching implications for cellular function and for responsiveness and resistance to the drugs. Experiments to characterize the effects of lithium and valproate on these genes are in progress.

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