INOSITOL METABOLISM IN PEDIATRIC BIPOLAR DISORDER
Kim M. Cecil, Nick C. Patel, and Melissa P. DelBello

Summary

Abnormalities within the phosphatidylinositol signaling pathway have been hypothesized to underlie the neurophysiology of bipolar disorder. The precise mechanism of action by which mood-stabilizing medications, such as lithium, anticonvulsants, and atypical antipsychotics, provide therapeutic benefit in patients with bipolar disorder remains unknown. In this review, the authors’ intent is to summarize the literature relevant to inositol metabolism, discuss the inositol depletion hypothesis with respect to pediatric bipolar disorder and offer future directions for the field. The “inositol depletion” hypothesis provides one explanation for the therapeutic effects of mood stabilizers. Knowledge of the mechanisms of action of agents used to treat bipolar disorder is critical since this may lead to a better understanding of neuropathology of bipolar disorder and the development of more effective treatment options. Magnetic resonance spectroscopy has been used to investigate the in vivo alterations of inositol metabolism in patients with bipolar disorder. Additionally, a few studies have examined the effects of treatments on inositol metabolism. A small number of these studies included children and adolescents, which offers additional insight towards understanding the role of the phosphatidylinositol pathway in bipolar disorders.


Declaration of interest: This work was supported by grant funding from the National Institutes of Health (P01 ES011261 (KMC), R21 ES013524 (KMC), R01 CA112182 (KMC), K23 MH063373 (MPD), the United States Environmental Protection Agency (R82938901 (KMC), and the Thrasher Research Fund (02822-2 (NCP).

Kim M. Cecil, PhD1, Nick C. Patel, PharmD, PhD2 and Melissa P. DelBello, MD3
1Imaging Research Center and the Department of Radiology, Cincinnati Children’s Hospital Medical Center, 2Division of Pharmacy Practice, University of Cincinnati College of Pharmacy, and 3Division for Bipolar Disorders Research, University of Cincinnati College of Medicine

Corresponding Author
Kim M. Cecil, PhD, Cincinnati Children’s Hospital Medical Center, Department of Radiology, MLC 5031, 3333 Burnet Avenue, Cincinnati, OH 45229. Telephone: 513/636-8559; FAX: 513/636-3754; Email: kim.cecil@cchmc.org

Introduction

The recognition of bipolar disorder in childhood and adolescence offers a unique opportunity to explore the underlying neurobiology and biochemistry of this disorder without having to also account for the consequences of long-term treatment effects and chronic illness course. For several decades, inositol metabolism has been implicated as having a significant role in the etiology and treatment effects of bipolar disorder, primarily due to the therapeutic response of lithium in bipolar patients. Proton and phosphorus magnetic resonance spectroscopy (MRS) techniques provide non-invasive methods for measuring select constituents involved with inositol metabolism. Unfortunately, few studies of children and adolescents with bipolar disorders have examined inositol metabolism with MRS techniques. The goals of this article are to summarize the literature relevant to inositol metabolism, discuss the inositol depletion hypothesis with respect to pediatric bipolar disorder and offer future directions for the field.

Biochemistry of Inositol

A biochemical cascade often referred to as the phosphatidylinositol (PI) cycle provides important signal functioning via the generation of second-messengers. Myo-inositol (m1) is the principal substrate for synthesis of the membrane lipid phosphatidylinositol (PI). PI, while more abundant, maintains an equilibrium with its phosphorylated forms, phosphatidylinositol 4-phosphate (PIP) and phosphatidylinositol 4,5-bisphosphate (PIP2). The receptor-triggered hydrolysis of PIP2 converts extracellular signals into intracellular ones, which are essential for neuronal communication. In neurons, the PI cycle is initiated via
guanine nucleotide protein (G) coupled, ligand binding of serotoninergic (5-HT<sub>1c</sub> and 5-HT<sub>1a</sub>), glutaminergic (mGlu<sub>4</sub> and mGlu<sub>5</sub>), dopaminergic (D<sub>1</sub>), cholinergic (M<sub>1</sub> and M<sub>3</sub>) and adrenergic (α<sub>1A</sub> and α<sub>1P</sub>)(Fisher et al. 1992) illustrated in Figure 1, an agonist binds to a receptor complex, which consists of the specific type of receptor, G-protein and phospholipase C (PLC). This binding leads to the PLC-catalyzed breakdown of PIP<sub>2</sub> into the second messengers, 1,2-diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (Ins<sub>1,4,5</sub>IP<sub>3</sub> or generically IP<sub>3</sub>). Ins<sub>1,4,5</sub>IP<sub>3</sub> subsequently binds to specific receptors on the endoplasmic reticulum (ER) causing the release of stored intracellular calcium (Ca<sup>2+</sup>). Ins<sub>1,4,5</sub>IP<sub>3</sub> can also be formed via enzymatic dephosphorylation of inositol hexaphosphate (IP<sub>6</sub>) with multiple inositol polyphosphate phosphatase (mIP<sub>P</sub>). This pathway is negatively regulated by prolyl oligopeptidase (PO). IP<sub>6</sub> is sequentially dephosphorylated into inositol bisphosphates (IP<sub>2</sub>), inositol monophosphates (IP<sub>1</sub>) and finally, into IP<sub>1</sub> via inositol-1,4 bisphosphate 1-phosphatase (IPP) and inositol monophosphatase (IMPase), respectively. Myo-inositol also synthesized de novo from glucose-6-phosphate (G-6-P), via an IP<sub>1</sub> intermediate and myo-inositol-1-phosphate synthase (INO1). A high affinity mI transport system has been characterized in select cell types, including neurons. The sodium/myo-inositol cotransporter (SMIT) may also provide another source of mI depletion to the cell.

**Inositol Depletion Hypothesis**

One hypothesized mechanism by which lithium exerts antimanic effects is known as the “inositol depletion” hypothesis. This hypothesis, proposed by Berridge et al. (Berridge et al. 1982), suggested that lithium exerts mood stabilization through the competitive inhibition of IMPase, resulting in decreased mI concentrations (Allison and Stewart 1971). It has been postulated that lithium may also reduce mI concentrations through the inhibition of IPP, as well as inhibition of SMIT (Harwood 2005, Wolfson et al. 2000).

Since IMPase regenerates inositol from IP<sub>1</sub>, inhibition of this enzyme depletes inositol. The accumulation of nonmessenger inositol phosphates prevents synthesis of inositol which is needed for renewal of PIP<sub>2</sub> and subsequently, DAG and IP<sub>3</sub> after repeated receptor activation. The addition of exogenous inositol appears to reverse the effects of lithium, which suggests inositol depletion as a potential mechanism of action of lithium. In vitro, the combination of lithium and valproic acid appears to enhance the effect of lithium alone, indicating that each drug may inhibit the same signal transduction pathway at different points. (Williams et al.

---

**Figure 1.** A biochemical schematic diagram illustrates the key aspects of inositol metabolism implicated in bipolar disorders

Abbreviations: agonist (A), receptor complex (R), which consists of the given type of receptor, guanine nucleotide protein (G), and phospholipase C (PLC), 1,2-diacylglycerol (DAG), phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>), phosphatidylinositol 4-phosphate (PIP), phosphatidylinositol (PI), myo-inositol (mI), inositol monophosphatase (IMPase), inositol monophosphates (IP<sub>1</sub>), inositol-1,4 bisphosphate 1-phosphatase (IPP), inositol bisphosphates (IP<sub>2</sub>), inositol-1,4,5-trisphosphate (Ins<sub>1,4,5</sub>IP<sub>3</sub>), or generically IP<sub>3</sub>), endoplasmic reticulum (ER), intracellular calcium (Ca<sup>2+</sup>), hexaphosphate (IP<sub>6</sub>), multiple inositol polyphosphate phosphatase (mIP<sub>P</sub>), prolyl oligopeptidase (PO), glucose-6-phosphate (G-6-P), myo-inositol-1-phosphate synthase (INO1), sodium/myo-inositol cotransporter (SMIT), with the drugs lithium (Li), valproate (VPA), carbamazepine (CBZ) site of action indicated with orange boxes with four sided arrows.
2002) However, if the inhibition of IMPase is sufficient to deplete inositol and subsequently, PIP₃, then, it would halt formation of the second messengers IP₃ and DAG. The net result would be the inhibition of transmembrane signaling. While in vitro investigations have demonstrated the inhibitory effects of lithium on IMPase, in vivo measurements have not consistently revealed an inhibition of PI signaling. However, there is some evidence for localized effects of lithium on PI signaling within the brain. The implications of changes in brain mI concentrations may be extensive, as the PI cycle is involved in the regulations of various cellular activities, including intracellular calcium mobilization, protein kinase C activity, gene expression and cytoskeletal changes (Harwood 2005, Moore et al. 2000).

Magnetic Resonance Spectroscopy of Bipolar Disorder

In vivo MRS provides a non-invasive imaging technique useful for quantitative measurements of specific neurochemicals, such as inositol and inositol phosphates, from localized brain regions. Therefore, the neurochemical abnormalities associated with bipolar disorder can be investigated. Most studies of bipolar disorder have employed proton (¹H) and phosphorus (³¹P) MRS techniques (Strakowski et al. 2000) When reviewing the MRS literature, it is important to note the quantification methods employed in the study. The initial MRS studies reported neurochemical changes in the form of metabolite ratios. Typically, a simple comparison of metabolite peak areas with a basis peak, usually the composite creatine (Cr), where Cr in proton MRS studies represents both creatine and phosphocreatine, assumed constant. As the field matured, investigators compared metabolite levels to internal water concentrations or external phantoms as reference standards. Eventually, sophisticated computer software allowed modeling of phantom solutions to determine metabolite concentrations. Current studies report metabolite concentrations with various corrections for tissue contributions (gray, white, cerebrospinal fluid (CSF)), coil factors, voxel sizes, and other pulse sequence dependent factors such as metabolite relaxation rates.

Studies of adults with bipolar disorder alterations in frontal and temporal mI in manic and depressed adults (Silverstone et al. 2005). However, euthymic bipolar adults do not exhibit abnormalities in mI concentrations, suggesting that mI alterations are either affective state specific or effective treatments normalize abnormalities. MRS studies of children and adolescents with bipolar disorder report abnormalities in mI levels. Davanzo and colleagues reported elevated mI/Cr in the anterior cingulate of manic bipolar children as compared to children with intermittent explosive disorder and healthy controls suggesting that this finding may represent a disease specific biomarker of abnormalities in second messenger pathways (Davanzo et al. 2003). Similarly, Cecil and colleagues reported a 16% elevation in ventral prefrontal gray matter mI concentrations in children at risk for developing bipolar disorder (children with a mood disorder and a bipolar parent) as compared to healthy children (Cecil et al. 2002). This indicated elevated mI levels may represent a susceptibility biomarker for pediatric bipolar disorder. The participants in this study were unmedicated and free of active mood symptoms at the time of the scan.

In contrast, Chang and colleagues reported that compared with healthy children and adolescents, stable medicated bipolar children and adolescents with a bipolar parent exhibited decreased right dorsolateral prefrontal cortex (DLPFC) N-acetyl aspartate to creatine-phosphocreatine (NA/A/Cr-PCr) levels. (Chang et al. 2003) This study failed to find differences in mI levels in DLPFC between bipolar and healthy youth, suggesting that the elevated mI reported in other studies may be specific to ventral and anterior cingulated prefrontal regions. In summary, in contrast to studies of bipolar adults, elevated prefrontal mI has been reported in bipolar youth, suggesting that elevations in mI may be a marker of early illness development or progression that diminishes with aging or related episodes. However, lithium and valproate may decrease mI, at least during initial exposure, and thus, differences in medication exposure may have contributed to the findings. Alternatively, differences in the affective states of patients among studies may also account for variability in the results (DelBello et al. 2006).

As discussed earlier, the ability of the cell to maintain sufficient mI for re-synthesis of PI is crucial for second messenger functioning. An elevation of mI, as found in manic and children at risk for developing bipolar disorder, suggests a disruption occurs in the re-synthesis of PI.

Consistent with ¹H MRS findings, ³¹P MRS studies, with limited sensitivity and spatial resolution and requiring larger voxel sizes than ¹H MRS, have reported that adults with bipolar disorder exhibit abnormalities in phospholipid and high-energy phosphate metabolism (Strakowski et al. 2000). Specifically, the phosphonoester (PME) peak observed in ³¹P MRS studies is a composite of phosphocholine, phosphoethanolamine, glycerol-3-phosphate, L-phosphoserine, and phosphoinositol, which are precursors of membrane phospholipids. As previously discussed, lithium inhibits inositol monophosphatase thereby increasing IP₃. Indeed, chronic administration of lithium in studies of rats and cats initially increases the PME peak due to the increase in IP₃ (Preece et al. 1992, Renshaw et al. 1986a, Renshaw et al. 1987, Renshaw et al. 1986b). In contrast, Silverstone and colleagues did not observe changes in PME/Phosphocreatine peak ratios in healthy subjects following lithium administration (Silverstone et al. 1996). Studies examining bipolar patients using both ¹H and ³¹P MRS in the same regions of interest are needed to clarify mechanisms and predictors of response to medications. Moreover, to our knowledge there have been no published ³¹P MRS studies of bipolar youth.

Effects of Mood Stabilizer Treatment on Brain Myo-Inositol Concentrations

Among the treatments commonly used for pediatric bipolar disorder, lithium has been the most extensively studied with regard to its effects on mI concentrations in the brain.
Lithium

Open-label studies have demonstrated the effectiveness of lithium as monotherapy for children and adolescents with acute mania (Kafantarlis et al. 2003, Kowatch et al. 2000) and bipolar depression (Patel et al. 2006). As previously discussed, evidence supporting the inositol depletion hypothesis arises from lithium’s ability for mood stabilization via reduction of mI concentrations (Berridge et al. 1982, Allison and Stewart 1971). Administration of lithium results in significant axonal growth cone spreading, a process thought to be mediated by changes in the PI signaling pathway because it is reversed by the addition of mI (Williams et al. 2002).

Davanzo and colleagues (Davanzo et al. 2001) measured changes in mI/Cr ratios in the anterior cingulate cortex following lithium therapy for one week in 11 children and adolescents (mean age 11.5 years) experiencing a manic, hypomanic, or mixed episode. The mean lithium level at week 1 was 0.64 mEq/L. Acute lithium treatment resulted in a significant reduction in anterior cingulate cortex mI/Cr ratios from baseline (1.1±0.6) to week 1 (0.8±0.3, p=0.05). There are no MRS studies evaluating the temporal effects of lithium in acutely manic adults. Studies of adult healthy volunteers have consistently demonstrated no temporal effects of lithium on mI concentrations in the dorsolateral prefrontal cortex and temporal lobe (Brambilla et al. 2004, Silverstone et al. 1996, Silverstone et al. 1999).

In contrast, Chang et al. (Chang et al. 2003) reported no significant difference in dorsolateral prefrontal cortex mI/Cr ratios in euthymic bipolar children and adolescents (mean age 12.6 years) compared to healthy controls. In this particular study, 36% of bipolar youths had exposure to lithium, but medications at the time of scanning were not provided. Euthymic bipolar adults receiving lithium exhibited normalized mI concentrations in the anterior cingulate cortex, dorsolateral prefrontal cortex, and temporal lobe (Brambilla et al. 2005, Moore et al. 2000, Silverstone et al. 2002). However, a small study of four adult bipolar patients being treated with lithium showed increased mI/Cr ratios in the basal ganglia compared with healthy controls (Sharma et al. 1992).

The effects of lithium on brain mI concentrations in children and adolescents with acute mania may not be applicable to those with bipolar depression, as mI concentrations may be affective state dependent (Silverstone et al. 2005). In combination with the 6-week, open-label study of lithium in adolescent bipolar depression (Patel et al. 2006), 28 adolescents (mean age 15.5 years) also received MRS scans at baseline, day 7, and day 42 of treatment to evaluate the acute and chronic effects of lithium on medial, and left and right lateral ventral prefrontal mI concentrations (Patel et al. 2005). The mean maximum serum lithium level was 1.1 mEq/L, and the mean endpoint serum lithium level was 0.9 mEq/L. Medial prefrontal cortex concentrations of mI on day 7 (4.7±0.6 IU) and day 42 (5.0±0.6 IU) were no different than baseline concentrations (4.9±0.5 IU). However, day 42 concentrations were significantly higher than those on day 7 (p=0.02). In the right lateral ventral prefrontal cortex, similar results were found as day 7 (4.0±0.7 IU) and day 42 concentrations (4.4±0.7 IU) were no different than baseline concentrations (4.3±0.7 IU). Day 42 concentrations were significantly higher than those on day 7 (p=0.02). These findings indicate that in bipolar depressed adolescents, the mechanism by which lithium exerts antidepressant activity may not be consistent with the inositol depletion hypothesis. The acute effects of lithium on brain mI concentrations, albeit nonsignificant in this study, may not be sustained with continued administration.

Few MRS studies in adult patients with bipolar depression have examined the chronic effects of lithium treatment on mI concentrations. Moore et al. (Moore et al. 1999) reported lower frontal lobe mI concentrations following acute (5-7 days) and chronic lithium administration (3-4 weeks) compared to baseline concentrations. No significant changes in mI concentrations were observed in the occipital, parietal, or temporal regions. Friedman et al. (Friedman et al. 2004) observed significant increases in regional gray matter mI concentrations with chronic lithium treatment (2-7 months). There are two key points about these adult studies that warrant discussion. First, in the Moore et al. (Moore et al. 1999) study, frontal lobe mI concentrations at the acute and chronic time points were not different from baseline when Bonferroni correction was applied for multiple comparisons. Second, in the Friedman et al. (Friedman et al. 2004) study, no MRS scan was performed early in treatment and therefore, it is unknown whether adult bipolar depressed patients experienced acute reductions in regional gray matter mI concentration followed by subsequent increases.

Valproate (including divalproex sodium)

Among youths with acute mania, treatment with divalproex sodium (which dissociates to valproate in the gastrointestinal tract) is effective with high response rates (53% to 74%) and is fairly well-tolerated (Kowatch et al. 2000, Pavuluri et al. 2005, Wagner et al. 2002). The mechanism by which valproate achieves mood stabilization is unknown, but it appears that valproate’s therapeutic effects may be mediated through increased turnover of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), with potentiation of GABAergic functions, blockade of cell firing induced by N-methyl-D-aspartate-type glutamate receptors, and attenuation of protein kinase C isoenzymes. Valproate has been shown to cause mI depletion, although the mechanism by which valproate does so may be different from that of lithium. Specifically, valproate has been shown to decrease activity of INO1, the enzyme responsible for the conversion of G-6-P, which is the rate limiting step in de novo synthesis of inositol (Shaltiel et al. 2004). In addition, valproate may have modulatory effects on PO (Cheng et al. 2005) and inhibitory effects on SMIT (Harwood 2005, Wolfson et al. 2000), both altering concentrations of brain mI. Like lithium, valproate administration results in axonal growth cone spreading (Williams et al. 2002).

In an unpublished study of eight children with bipolar disorder (mean age 10.4 years), no significant difference was observed in mI/Cr ratios in the anterior cingulate cortex before and after divalproex sodium
Table 1. Summary of pediatric bipolar MRS studies examining treatment effects on brain ml concentrations* †

<table>
<thead>
<tr>
<th>Reference</th>
<th>Medication</th>
<th>Duration (wks)</th>
<th>N</th>
<th>Clinical status</th>
<th>Region</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davanzo et al. 2001</td>
<td>Li</td>
<td>1</td>
<td>11</td>
<td>Manic, hypomanic, or mixed</td>
<td>ACC</td>
<td>ml ↓</td>
<td>Prior exposure to medications reported; comparison with 11 healthy controls</td>
</tr>
<tr>
<td>Chang et al. 2003</td>
<td>Li, VPA, CBZ</td>
<td>-</td>
<td>15</td>
<td>Euthymic</td>
<td>DLPFC</td>
<td>ml ↔</td>
<td>Day 42 &gt; day 7, day 42 = day 0</td>
</tr>
<tr>
<td>Patel et al. 2005</td>
<td>Li</td>
<td>6</td>
<td>28</td>
<td>Depressed</td>
<td>MPFC, L/R LVPC</td>
<td>ml ↔</td>
<td></td>
</tr>
<tr>
<td>Davanzo et al. 2002</td>
<td>DVP</td>
<td>Variable</td>
<td>8</td>
<td>Mood state not reported</td>
<td>ACC</td>
<td>ml ↔</td>
<td></td>
</tr>
<tr>
<td>Chang et al. 2005</td>
<td>LG</td>
<td>8</td>
<td>11</td>
<td>Depressed</td>
<td>DLPFC</td>
<td>ml ↑</td>
<td></td>
</tr>
<tr>
<td>DelBello et al. 2005</td>
<td>OLZ</td>
<td>4</td>
<td>19</td>
<td>Manic or mixed</td>
<td>MPFC, L/R LVPC</td>
<td>ml ↔</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: ACC = anterior cingulate cortex; CBZ = carbamazepine; DLPFC = dorsolateral prefrontal cortex; DVP = divalproex sodium; Li = lithium; L/R LVPC = left and right lateral ventral prefrontal cortex; LTG = lamotrigine; ml = myo-inositol; MPFC = medial prefrontal cortex; OLZ = olanzapine; VPA = valproate; wks = weeks.
†Change in ml concentrations: increased (↑), decreased (↓), no change/difference (+−).

Treatment (Davanzo et al. 2002). Serum valproate levels were not provided and duration of divalproex sodium treatment was variable across subjects. This is consistent with previous adult findings of Friedman et al. (Friedman et al. 2004) and Moore et al. (Moore et al. 2000), which showed no significant temporal changes in regional gray matter or anterior cingulate cortex ml concentrations with chronic valproate treatment. In the Chang et al. (Chang et al. 2003) study reporting similar dorsolateral prefrontal cortex ml/Cr ratios in euthymic bipolar and healthy controls, 64% of bipolar youths had previous exposure to valproate. MRS studies of euthymic bipolar adults on divalproex sodium have also shown normalization of anterior cingulate cortex and temporal lobe ml concentrations (Moore et al. 2000; Silverstone et al. 2002). A study of manic and mixed bipolar adults receiving divalproex sodium, as monotherapy or in combination with other psychotropic medications, reported no difference in frontal lobe ml concentrations compared with healthy controls (Cecil et al. 2002).

Other anticonvulsants
Although carbamazepine may be effective in children and adolescents with acute mania (Moore et al. 2000, Silverstone et al. 2002), it is generally considered a second-line treatment option. Carbamazepine’s mood-stabilizing properties may be related with its modulatory activity at sodium and calcium channels, as well as GABA receptors. Similar to lithium and valproate, carbamazepine has been shown to possess inhibitory activity at the SMIT (Wolfson et al. 2000) and causes axonal growth cone spreading at therapeutic concentrations (Williams et al. 2002). No MRS studies examining the temporal effects of carbamazepine on brain ml concentrations in pediatric or adult bipolar patients are available. In the Chang et al. (Chang et al. 2003) study discussed previously, 14% of euthymic bipolar youths had exposure to carbamazepine treatment.

Lamotrigine has preliminary data from two open-label studies of bipolar depressed adolescents suggesting clinical benefit (Chang et al. 2006, Swope et al. 2004). The mechanism of action of lamotrigine in bipolar patients may be associated with inhibition of sodium and calcium channels in presynaptic neurons and resulting stabilization of the neuronal membrane. There are no published in vitro data to suggest that lamotrigine possesses pharmacological activity involving the PI signaling pathway. Furthermore, lamotrigine does not cause axonal growth cone spreading (Harwood 2005). A recent MRS study by Chang et al. (Chang et al. 2006) examined the effects of lamotrigine on ml concentrations in the left dorsolateral prefrontal cortex of 11 adolescents (mean age 16.1 years) with bipolar I, II, or NOS, and experiencing a depressive episode. Over 8-week, open-label lamotrigine treatment (mean dose 136±28 mg/day), a significant increase was detected in left dorsolateral prefrontal cortex ml/Cr ratios (0.49±0.06 to 0.56±0.11, p=0.038). This open-label trial of lamotrigine did allow for adjunctive psychotropic medications in three patients: one taking aripiprazole, one taking valproate, and one taking methylphenidate. No MRS studies examining the effects of lamotrigine on brain ml concentrations in adults with bipolar disorder have been conducted.

Atypical antipsychotics
Open-label studies of olanzapine have demonstrated beneficial effects in children and adolescents
with bipolar disorder (Biederman et al. 2005, DelBello et al. 2005, Frazier et al. 2001). Olanzapine, an atypical antipsychotic whose purported mechanism of action includes serotonin-2A (5HT₂A) and dopamine-2 (D₂) receptor antagonism, is not believed to affect the PI signaling pathway. DelBello et al. (DelBello et al. 2005) reported that treatment with olanzapine (mean dose 12.7±4.8 mg/day) over a 28-day period did not significantly affect mI concentrations in the medial, and left and right lateral ventral prefrontal cortices of 19 adolescents (mean age 14.1 years) with bipolar I disorder, manic or mixed episode. Other atypical antipsychotics, such as aripiprazole, quetiapine, risperidone, and ziprasidone, may not affect prefrontal mI concentrations as their mechanisms of action also include 5HT₂A and D₂ receptor antagonism. There are no MRS studies of adult bipolar patients examining change in brain mI concentrations with atypical antipsychotics; one study of risperidone in 14 adults with chronic schizophrenia reported increased mI/Cr ratios in the thalamus, but not in the frontal or temporal lobes (Szulc et al. 2005).

**Summary of treatment effects on brain inositol metabolism**

To date, data from MRS studies examining mood stabilizer treatment effects on brain mI concentrations in pediatric bipolar patients are fairly limited. Whether the inositol depletion hypothesis is a common mechanism by which medications for the treatment of pediatric bipolar disorder achieve mood stabilization remains unclear. The reported changes of brain mI concentrations with lithium and lamotrigine, however, do not fully support the inositol depletion hypothesis, particularly in adolescents with bipolar depression. For example, although acute reductions in mI concentrations with lithium are consistent with this hypothesis, chronic administration shows contrasting effects, suggesting that there may be alternate and/or multiple mechanisms by which lithium exerts therapeutic benefit in patients with bipolar disorder.

Results from the available studies may be confounded by differing methodologies. For example, changes in mI concentrations with mood stabilizer treatment may exhibit regional specificity in the brain, and the direction of change may be dependent on the type of mood episode. Concomitant psychotropic medications, variability in the duration of mood stabilizer treatment, and small samples under study may also limit the ability to make sound conclusions about a single agent’s effects on the PI signaling pathway. Also, quantification of brain mI concentrations with MRS is inherently confounded due to spectral overlap between mI, inositol monophosphates, and glycine at conventional magnetic field strengths at or below 1.5T (Deutsch et al. 1983, O’Donnell et al. 2003, Renshaw et al. 1986).

**Conclusions and Future Directions**

Studies examining bipolar patients, especially early onset pediatric patients, using both ¹H and ³¹P MRS in the same regions of interest are needed to identify the neurochemical traits of bipolar disorder and any differences dependent upon mood state. In contrast to studies of bipolar adults, elevated prefrontal mI has been reported in bipolar youth, suggesting that elevations in mI may be a marker of early illness development or progression that diminishes with aging or related episodes. If neurochemical markers were fully developed and validated with clinical features, such markers could guide early intervention for an individual patient. In conjunction with the diagnostic aspects, efforts to clarify mechanisms associated with and predictors of response to medications need consistent MRS methodologies and larger sample sizes. Currently, only lithium and lamotrigine have been shown by MRS studies to temporally alter select regional brain mI concentrations in children and adolescents with bipolar disorder. Changes with inositol metabolism and the PI signaling pathway may only represent a small aspect of bipolar disorder, with an intricate relationship of several cellular mechanisms comprising the basis of mood stabilizer treatment. Establishing neurochemical biomarkers associated with treatment would be of significant value in developing targeted interventions and reducing the morbidity and mortality associated with ineffective treatments.

**References**


Inositol Metabolism in Pediatric Bipolar Disorder


