Treatment of Adolescent Bipolar Depression with Lithium: Effects on Brain MyoInositol Levels Measured by Proton MR Spectroscopy

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Purpose: Abnormalities within the phosphoinositol (PI) signaling pathway have been hypothesized to underlie bipolar disorder. Supporting evidence for this hypothesis is that lithium, a mood stabilizer, may exert this effect by depleting neuronal *myo*-inositol (mI) levels through the inhibition of inositol monophosphatase (Hallcher and Sherman 1980), which results in the downregulation of the PI signaling pathway and dampening of overactive neurotransmission. Proton magnetic resonance spectroscopy (^{1}H MRS) studies have shown that manic or mixed patients with bipolar disorder have higher mI concentrations compared with healthy subjects, and that these raised concentrations may normalize with mood stabilizer treatment (Davanzo et al 2001; Davanzo et al 2003; Cecil et al 2002). *Myo*-inositol concentrations may be affective state dependent, with increased levels occurring with mania and decreased or normal levels occurring with bipolar depression (Silverstone et al 2005). Despite widespread use in treating adults with bipolar disorders, the neurochemical effects of lithium in adolescents with bipolar depression are largely unknown. This study used proton magnetic resonance spectroscopy (^{1}H MRS) to identify the *in vivo* effects of lithium on *myo*-inositol (mI) concentrations in adolescent bipolar depression.

Materials and Methods: Twenty-eight adolescents (12-18 years old) with bipolar I disorder, current episode depressed, received open-label lithium 30 mg/kg, adjusted to achieve serum levels of 1.0-1.2 mEq/L. Medial, left and right lateral prefrontal mI concentrations were measured at baseline, day 7, and day 42 using short echo (TE 35 ms), single-voxel MRS acquired at 1.5T. Concentrations of brain metabolites were determined using LC Model software (Provencher 1993). Metabolite concentrations were adjusted for amount of cerebral spinal fluid (CSF) in each voxel. Change in mI concentration over time was analyzed using likelihood-based mixed-model repeated measures analysis of variance (*proc mixed*). Baseline mI concentrations were compared between remitters and non-remitters.

Results: In the medial prefrontal cortex, a significant main effect for time was observed for mI concentrations ($F_{2,47} = 3.8$, $p = 0.03$). Concentrations of mI on day 42 were significantly higher than those of day 7 ($t = 2.5$, $p = 0.02$). A significant main effect for time was also found in right lateral prefrontal cortex mI concentrations ($F_{2,47} = 3.2$, $p = 0.05$), with day 42 concentrations being significantly higher than those on day 7 ($t = 2.5$, $p = 0.02$). *Myo*-inositol concentrations in the left lateral prefrontal cortex remained stable over time ($F_{2,46} = 0.7$, $p = ns$). At baseline, mI concentrations in the medial prefrontal cortex were significantly lower for remitters [4.6 mM (SD = 0.2)] compared to non-remitters [5.0 mM (SD = 0.5)] ($t = 3.3$, $p = 0.003$). There were no differences in baseline left ($t = 0.5$, $p = ns$) and right ($t = 0.4$, $p = ns$) lateral prefrontal cortex mI concentrations based upon remission status.

Conclusions: Medial and right lateral prefrontal mI concentrations may increase with chronic lithium treatment, paralleling improvement in depressive symptoms in adolescents with bipolar disorder. Further investigation of the effect of lithium on mI is warranted to better understand possible mechanisms by which lithium exerts its antidepressant activity, particularly in adolescents.

References:

Cecil KM, DelBello MP, Morey R, Strakowski SM (2002): *Bipolar Disord* 4:357-365

Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M, McCracken J (2001): *Neuropsychopharmacology* 24:359.

Davanzo P, Yue K, Thomas MA, Belin T, Mintz J, Venkatraman TN, et al (2003): *Am J Psychiatry* 160:1442-1452

Hallcher LM, Sherman WR (1980): *J Biol Chem* 255:10896-10901

Provencher SW (1993): *Magn Reson Med* 30:672-679

Silverstone PH, McGrath BM, Kim H (2005): *Bipolar Disord* 7:1-10