Neurochemical Effects of Olanzapine in Adolescent Mania: A Proton Magnetic Resonance Spectroscopy Study

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Introduction

Although little is known about the neurochemical effects of pharmacological treatments for bipolar disorder, preclinical reports suggest that olanzapine may have neurotrophic properties. We sought to identify the *in vivo* effects of olanzapine on N-acetyl-aspartate (NAA) levels using proton magnetic resonance spectroscopy (MRS). Secondary aims included identifying neurochemical predictors of successful olanzapine treatment and other neurochemical effects of olanzapine.

Methods

Twenty adolescents (aged 12-18 years) admitted for their first hospitalization for bipolar disorder, type I, manic or mixed, were recruited from consecutive admissions to the psychiatric units of an academic medical center. Ten demographically matched healthy subjects were recruited from the community. Medial and bilateral prefrontal regions were sampled using a short echo MRS acquisition (PROBE-P, General Electric Medical Systems, 1.5 T, echo time 35 msec, repetition time 2000 msec, 8 cc voxels). NAA, choline, *myo*-inositol, creatine/phosphocreatine, and glutamate/glutamine levels were quantified using LCModel (Provencher) and measured at three time points. Image segmentation of each voxel was performed using custom software to account for CSF and tissue contributions. Manic adolescents were scanned prior to receiving medication, and on days 7 and 28 of olanzapine monotherapy. Healthy subjects did not receive medication but underwent MRS at the same time points to assess for normal variability in metabolite concentrations between time points.

Results

Clinical remission was defined by an endpoint Young Mania Rating Scale score of $\leq$12 and an endpoint Clinical Global Impression Improvement score of $\leq$ 2. Eleven manic adolescents remitted following olanzapine treatment. Olanzapine remitters exhibited a greater increase over time in medial prefrontal NAA compared with non-remitters ($p=0.007$). Baseline medial prefrontal choline was greater in olanzapine remitters than in non-remitters ($t=-3.9$, $p=0.001$). Manic adolescents treated with olanzapine had an increase from baseline to day 7 in medial ($p=0.002$) and right lateral ($p=0.02$) prefrontal choline.

Conclusions

Successful treatment of mania with olanzapine may increase prefrontal neuronal viability. Additionally, olanzapine-induced increases in choline may initiate a cascade of events that leads to alteration of abnormalities in cell membrane metabolism or second messenger pathways that are thought to be involved in the pathophysiology of bipolar disorder.