Regional Cerebral Glucose Metabolic Abnormalities in Bipolar II Depression

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Background: Functional neuroimaging studies of bipolar disorder (BD) performed in conjunction with antidepressant treatment trials generally require that patients remain on mood stabilizers to reduce the risk of inducing mania; yet, it is unknown whether the metabolic abnormalities evident in unmedicated BD depressives remain detectable in patients receiving mood stabilizers. This study investigated whether cerebral metabolic abnormalities previously reported in unmedicated BD subjects are evident in depressed bipolar disorder type II (BD II) subjects receiving lithium or divalproex.

Methods: Using [^{18}F]-fluorodeoxyglucose-positron-emission tomography, cerebral glucose metabolism was compared between 13 depressed BD II subjects on therapeutic doses of lithium or divalproex and 18 healthy control subjects. Regional metabolism was compared between groups in predefined regions of interest.

Results: Metabolism was increased in the bilateral amygdala, accumbens area, and anteroventral putamen, left orbitofrontal cortex and right pregenual anterior cingulate cortex in depressives versus control subjects. Post hoc exploratory analysis additionally revealed increased metabolism in left parahippocampal, posterior cingulate, and right anterior insular cortices in depressives versus control subjects. Correlational analyses showed multiple limbic-cortical-striatal interactions in the BD sample not evident in the control sample, permitting sensitive and specific classification of subjects by discriminant analysis.

Conclusions: These results confirm previous reports that bipolar depression is associated with abnormally increased metabolism in the amygdala, ventral striatum, orbitofrontal cortex, anterior cingulate, and anterior insula, and extend these results to bipolar disorder type II depressives on lithium or divalproex. They also implicate an extended functional anatomical network known to modulate visceromotor function in the pathophysiology of BD II depression.

Key Words: Cerebral metabolism, bipolar disorder, depression, striatum, prefrontal cortex, amygdala, mood stabilizers

Bipolar disorder (BD) is a chronic, disabling condition with a reported 12-month prevalence of 1% to 3% (Kessler et al 2005). Much of the morbidity and mortality associated with BD is attributable to the depressive phase (Calabrese et al 2003), which manifests a substantially more chronic and severe course and higher suicide rate in bipolar disorder type II (BD II), as compared with bipolar disorder type I (BD I) depression (Judd et al 2003). Yet, little is known about the pathophysiology of BD II. Functional neuroimaging studies of mood disorders have shown that physiological activity is abnormal in limbic and paralimbic structures such as the amygdala, ventral anterior cingulate cortex (ACC), and anatomically related areas of the orbitofrontal cortex (OFC), striatum, and thalamus during major depressive episodes, but the majority of these studies focused on unipolar depression. Few neuroimaging studies have assessed neurophysiological activity in unmedicated subjects with bipolar depression, and none of the studies specifically have limited the study sample to BD II (reviewed in Ketter and Drevets 2002).

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Previous positron-emission tomography (PET) studies of unmedicated bipolar depressives that combined BD I and BD II cases demonstrated abnormally elevated metabolic activity in the amygdala, ventral striatum, and anatomically related limbic and paralimbic cortices. Drevets et al (1995a, 2002) found significantly increased normalized (regional/global) metabolism in the left amygdala, with a trend toward hypermetabolism in the right amygdala and the right ventral striatum in unmedicated bipolar depressives (n = 7, 4 BD II) relative to healthy control subjects. The same BD sample had decreased flow and metabolism in the subgenual ACC, an area where decreased perfusion also had been identified in an independent sample of bipolar depressives (Drevets et al 1997).

In a larger sample of unmedicated, treatment-resistant, bipolar depressives (n = 17, 13 BD II) who were moderately to severely depressed, Ketter et al (2001) also found increased normalized metabolism in the right amygdala, bilateral ventral striatum, medial thalamus, and the medial cerebellum relative to healthy control subjects. Ketter et al (2001) also reported that in mildly depressed BD cases (n = 16, 9 BD II), normalized metabolism was increased in the posterior cingulate cortex, left ventrolateral prefrontal cortex (PFC), left middle and superior frontal gyri, left insula, hippocampus, left postcentral gyrus, left transverse temporal gyrus, and cerebellum, and decreased in the right inferior and middle temporal gyri. This study also reported regional differences in absolute metabolism, but the interpretation of these data was confounded by a significant reduction in whole brain metabolism in BD subjects relative to control subjects. Moreover, it was noteworthy that studies of unmedicated bipolar depressives identified abnormally increased normalized metabolism in many of the same regions where metabolism was elevated in unmedicated unipolar depressives, including the amygdala, ventral striatum, medial thalamus, ventrolateral PFC, OFC, pregenual ACC,

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anterior insula, posterior cingulate cortex, and medial cerebellum (reviewed in Drevets 2000).

Insofar as these abnormalities constitute biologically relevant targets for treatment, the ability to assess how they are affected by antidepressant treatments is an important goal in investigations aimed at elucidating therapeutic mechanisms. However, the risk that such treatments would trigger hypomanic or manic conversion in BD cases generally requires that such subjects receive mood stabilizers during antidepressant treatment trials. It remains unclear, however, whether the metabolic abnormalities described above would be evident in subjects receiving mood-stabilizing agents. Antidepressant, antipsychotic, and antianxiety treatments have been reported to reduce cerebral blood flow and metabolism in some frontal, parietal, and temporal lobe regions, such that many studies of patients on these medications have not detected areas of abnormally elevated metabolism or instead have reported areas of reduced flow or metabolism not evident in studies of unmedicated samples (reviewed in Drevets 2000).

Preliminary data in the study conducted by Drevets et al (2002) suggested that mood stabilizer treatment reduced amygdalar metabolic activity toward normative levels in a small sample of clinically remitted subjects with BD but mood stabilizer treated subjects who remained depressed were not studied. More recently, Bauer et al (2005) found that currently depressed BD patients (n = 10, 1 BD II) being medicated with a combination of antidepressants and mood stabilizers exhibited increased relative metabolism versus control subjects in the subgenual ACC, right amygdala, right hippocampus, right ventral striatum, left thalamus, and cerebellar vermis, and decreased metabolism in the middle frontal gyri bilaterally. However, the variability in type, combination, and dosage of medications and the lack of blood drug concentrations (to ensure that therapeutic levels were achieved) limited the interpretability of these data.

The current study used [^{18}F]-fluorodeoxyglucose (^{18}FDG) PET to assess cerebral metabolic rates for glucose (CMRglu) in BD II patients who remained depressed while receiving therapeutic doses of mood stabilizers. Based on previous PET studies of unmedicated depressed patients and preclinical studies of lithium and divalproex sodium (Bauer et al 2005; Drevets et al 2002; Du et al 2003; Ketter et al 2001), BD II depressives on therapeutic levels of mood stabilizers in the current study were expected to exhibit abnormally elevated metabolic activity in similar regions as found in unmedicated depressed samples, including the amygdala and anatomically related areas of the orbital and medial PFC and the ventral striatum. Associations between regional glucose metabolism and depression and anxiety ratings were examined post hoc.

Methods and Materials

Subjects

Patients (n = 13; 11 female subjects) met DSM-IV criteria for BD type II and for a current major depressive episode. Healthy control subjects (n = 18, 15 female subjects) with no history of psychiatric illness also participated. Diagnoses were established by an unstructured interview with a psychiatrist and the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P) with a second clinician. Patients were included if they had an initial score of ≥20 on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). Severity of anxiety symptoms also was rated using the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959). All ratings were obtained on the day of the PET scan. Exclusion criteria included current psychotic features, serious suicidal risk, substance abuse within 90 days, substance dependence within 5 years, rapid cycling course within 12 months, major medical or neurological disorders, pregnancy, and lactating female subjects. Patients were recruited as part of a clinical trial studying the effect of adding an adjunct antidepressant medication to mood stabilizer treatment and were required to take a stable dose of either divalproex sodium or lithium for at least 4 weeks, during which two weekly blood drug levels fell within the therapeutic range before imaging (plasma valproic acid concentrations of 50 to 125 ug/mL; serum lithium concentrations of .6–1.2 mEq/L). Other psychotropic medications and all medications likely to influence cerebral physiology, perfusion, or metabolism were not permitted within 2 weeks of scanning. Subjects provided written informed consent, as approved by the National Institute of Mental Health Institutional Review Board (NIMH-IRB).

Image Acquisition

Quantitative whole brain and regional metabolic measures were obtained using a technique that combined left cardiac ventricular chamber time-activity curve data with venous blood sampling to yield the input function for calculating CMRGlu. This method previously was validated against methods that employed arterial blood sampling to generate the ^{18}FDG input function (Moore et al 2003). Positron-emission tomography images were acquired using a GE Advance PET scanner (GE Medical Systems, Waukesha, Wisconsin) (35 contiguous slices 4.25 mm thick; axial resolution = 4.9 and 5.3 mm full-width at half maximum [FWHM] in two-dimensional [2-D] and three-dimensional [3-D] modes, respectively). Subjects received 4.5 mCi of ^{18}FDG following a fasting period of at least 6 hours. Following an initial transmission scan of the chest to permit measured attenuation correction of the cardiac emission scan, a 35-minute dynamic emission scan of the heart was acquired in 2-D mode (10 30-second frames and 10 3-minute frames), with concurrent serial venous blood sampling beginning 15 minutes posttracer injection. At 45 minutes posttracer injection, a 10-minute static emission scan of the brain was acquired in 3-D mode, which immediately was followed by an 8-minute transmission scan of the head to perform measured attenuation-correction of the emission scan.

An anatomical magnetic resonance image (MRI) was obtained for each subject using a 3.0 Tesla GE Signa Scanner (GE Medical Systems, Waukesha, WI) and a 3-D MPRAGE (echo time [TE] = 2.982 milliseconds, repetition time [TR] = 7.5 milliseconds, inversion time = 725 milliseconds, voxel size = .9 × .9 × 1.2 mm) for co-registration of PET images.

Image Analysis

To quantify whole brain and regional CMRGlu from ^{18}FDG emission images, the cardiac input function was derived by combining left cardiac ventricular chamber time-activity curve data with venous blood sampling, as detailed in Moore et al (2003). Briefly, cardiac slices were reconstructed and five left ventricular slices were identified for region-of-interest (ROI) placement. The cardiac image frames acquired from 0 to 5 minutes initially were averaged to allow localization of the left ventricular blood pool, while the frames acquired between 25 and 35 minutes permitted identification of myocardial wall ^{18}FDG uptake. Circular ROIs of 2 cm diameter were positioned over the left ventricular chamber on difference images obtained by subtracting the left ventricular myocardial ^{18}FDG uptake from the blood pool image to minimize spillover of radioactivity from the myocardium. An average left ventricular time-activity curve