Utilization of MRS to Identify Neurochemical Abnormalities in Patients With Bipolar Disorder

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The number of magnetic resonance spectroscopy studies that assess the levels of different neurochemicals in bipolar disorder has increased considerably in recent years. Abnormalities were reported mainly in the brain regions implicated in the pathophysiology of BD: the dorsolateral prefrontal cortex, cingulated gyrus, hippocampus and basal ganglia. Although these findings are not diagnostic, future research in this area may help to elucidate the pathophysiology of BD and monitor treatment effects.

Magnetic resonance spectroscopy (MRS) is a useful, noninvasive method of examining alterations in brain neurochemistry that might be associated with the development of bipolar disorder (BD) and the effects of treatment (Soares et al., 1996). It uses the same technology as magnetic resonance imaging and provides a frequency signal intensity spectrum of multiple peaks that reflect the metabolite levels of a localized region in the brain. Magnetic resonance spectroscopy data are usually displayed in the frequency domain, and the area under a specific peak is proportional to the number of protons processing at that frequency (Stanley, 2002). It can assess chemicals containing phosphorus-31 ($^{31}\text{P}$), carbon-13 ($^{13}\text{C}$), lithium-7 and fluorine-19. The most commonly used, however, is proton magnetic resonance spectroscopy ($^{1}\text{H}$-MRS).

$^{1}\text{H}$-MRS Studies

N-acetylaspartate (NAA) is the predominant resonance in the $^{1}\text{H}$-MRS spectrum of the normal adult human brain. It is an amino acid found in high concentrations in mature neurons and considered to be a marker of neuronal integrity and viability. Reductions in NAA may also reflect impairment in the formation and maintenance of myelin and mitochondrial energy production (Baslow, 2002). In adults with BD, decreased NAA levels were reported in the dorsolateral prefrontal cortex (DLPFC) (Winsberg et al., 2000), orbital frontal gray matter (Cecil et al., 2002) and hippocampus (Bertolino et al., 2003; Deicken et al., 2002). Lower DLPFC NAA levels were also reported in children (Chang et al., 2003) and adolescents (Kusumakar et al., 2002) with BD. Investigating treatment-induced effects, the administration of lithium (Eskalith, Lithobid) during a four-week period was shown to increase brain NAA concentration as indirect evidence of its neurotrophic/neuroprotective effects (Moore et al., 2000; Silverstone et al., 2003). This increase has not been demonstrated with divalproex (Depakote) (Silverstone et al., 2003).

Lithium and divalproex were also recently shown to be protective against dextroamphetamine (a human model of mania)-induced choline decrease (Silverstone et al., 2004). The choline (Cho) peak in the $^{1}\text{H}$-MRS is considered a potential biomarker for the status of membrane phospholipid metabolism, and basal ganglia Cho/creatine (Cr) is elevated in the euthymic (Kato et al., 1996; Sharma et al., 1992) and depressive state (Hamakawa et al., 1998) in patients with BD. Lithium treatment did not appear to alter Cho resonance in the parietal lobes in seven male patients compared to healthy controls (Stoll et al., 2002) or in the temporal cortex of healthy volunteers (Silverstone et al., 1999). In a case series (n=6), Stoll et al. (1996) demonstrated that oral Cho in combination with lithium was an effective therapy for some patients with treatment-refractory rapid-cycling BD.

Glutamate, glutamine and γ-aminobutyric acid (GABA) are also of interest, as antiglutamatergic and GABAergic anticonvulsants appear useful in treating BD. In a majority of MRS reports, the Glx region refers to glutamate and glutamine. In a group of adolescents with bipolar depression, a bilateral increase in Glx in the frontal cortex and basal ganglia has been reported (Castillo et al., 2000). Glutamatergic abnormalities may be involved in neurotoxicity that is potentially responsible for specific brain insults in BD. Decreased GABA levels were reported in the occipital cortex in nonmedicated patients with unipolar depression (Sanacora et al., 1999). Occipital cortex GABA concentrations after selective serotonin reuptake inhibitor (Sanacora et al., 2002) and electroconvulsive therapy treatment (Sanacora et al., 2003) were significantly higher than...
pretreatment concentrations. Patients with BD appear not to have such reduction in GABA levels (Mason et al., 2000).

Another important metabolite in 1H-MRS is myo-inositol (mI), which is a substrate for the phosphoinositide cycle. At therapeutic levels, lithium inhibits inositol monophosphatase and polyphosphate-1-phosphatase, which are involved in recycling inositol mono- and polyphosphates to mI (Berridge and Irvine, 1989). Divalproex also decreases the concentration of mI and increases the concentration of inositol monophosphate in rat brains (O'Donnell et al., 2003). Moore et al. (1999) found decreased mI in the right frontal lobe of depressed patients with BD following acute (five to seven days) lithium administration, which persisted through one month of treatment. However, the patients' clinical state was clearly unchanged at this time, supporting the hypothesis that the initial actions of lithium may occur with a reduction of mI and that this reduction initiates a cascade of secondary changes that are ultimately responsible for lithium's therapeutic efficacy. Consistent with this, Davanzo et al. (2001) observed a significant decrease in anterior cingulate mI/Cr ratios following seven days of lithium therapy in children and adolescents with early-onset BD. Children in a manic phase demonstrated elevated mI/Cr levels within the anterior cingulate cortex.

**31P-MRS Studies**

The 31P-MRS allows in vivo examination of the changes in phosphorus-based membrane metabolism and the effects of medication. In a comprehensive series of studies, one group measured frontal lobe phosphomonoesters (PMEs; precursors of membrane phospholipid metabolism) and demonstrated that frontal lobe PME levels vary with mood state (Deicken et al., 1995a; Kato et al., 1994, 1993). Deicken et al. (1995b) also reported significantly reduced PME in both the right and left temporal lobes in unmedicated euthymic patients compared with healthy controls. An increase in PME concentration with seven and 14 days of lithium administration in the human brain was observed (Yildiz et al., 2001). As patients in the previously mentioned studies were mostly on lithium or off lithium for short periods of time, increased levels of PME could reflect medication effects. This is significant, as lithium inhibits inositol monophosphatase, producing increased levels of PME that would be consistent with increased membrane anabolism.

**Conclusions**

Bipolar disorder is associated with altered brain chemistry in a number of regions, mainly the DLPFC, basal ganglia, hippocampus and anterior cingulate. The NAA levels in the DLPFC are decreased in patients with BD. It is not clear whether such an abnormality may precede illness onset, or to what extent it may reflect aberrant neurodevelopmental mechanisms, or whether it is related to progressive neuronal loss during the disease process. Decreased NAA levels may reduce the transfer of acetyl groups required for myelin formation and/or maintenance (Chakraborty et al., 2001). Moreno et al. (2001) demonstrated that NAA synthesis is coupled to energetic (glucose) metabolism using in vivo 13C-MRS and [1-13C] glucose infusion. Abnormal brain energy metabolism is also suggested by 31P-MRS findings, such as decreased phosphocreatine (PCr) and intracellular pH (Kato et al., 1994, 1993). A mitochondrial dysfunction hypothesis for the pathophysiology of BD has also been proposed (Konradi et al., 2004). Studying treatment effects on the neurochemistry of BD is an intriguing area of research (Soares, 2002). The findings of the studies reviewed here show that lithium increases total brain NAA and decreases mI in the anterior cingulate and right frontal lobe, whereas it does not affect the Cho resonance in the parietal lobes. Divalproex also appears to have an effect on the activity of the intracellular phosphoinositols cycle similar to lithium.

Treatment with GABAergic medications increases prefrontal GABA, while treatment with SSRIs is possibly associated with increased occipital cortex GABA concentrations and with a decrease in Cho in the anterior cingulate cortex. These findings are preliminary and need replication, but they are important. They reflect cellular metabolism and membrane turnover, upon which many essential neuronal functions, such as neurotransmission and second- messenger cascades, are dependent. The application of in vivo MRS technology to the study of the pathophysiology of BD and the mechanisms of action of mood stabilizers is a new field of research. Currently, this is primarily a research tool, but as research evolves and the mechanisms involved are elucidated, it is expected that such tools will be of relevance for diagnosing and monitoring the effects of various treatments.

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