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Short communication

Tissue-dependent cerebral energy metabolism in adolescents with bipolar disorder

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ABSTRACT

Objectives: To investigate tissue-dependent cerebral energy metabolism by measuring high energy phosphate levels in unmedicated adolescents diagnosed with bipolar I disorder.
Methods: Phosphorus-31 magnetic resonance spectroscopic imaging data were acquired over the entire brain of 24 adolescents with bipolar I disorder and 19 demographically matched healthy comparison adolescents. Estimates of phosphocreatine (PCr) and adenosine triphosphate (ATP, determined from the γ-resonance) in homogeneous gray and white matter in the right and left hemispheres of the cerebrum of each subject were obtained by extrapolation of linear regression analyses of metabolite concentrations vs. voxel gray matter fractions.
Results: Multivariate analyses of variance showed a significant effect of group on high energy phosphate concentrations in the right cerebrum ($p=0.0002$) but not in the left ($p=0.17$). *Post-hoc* testing in the right cerebrum revealed significantly reduced concentrations of PCr in gray matter and ATP in white matter in both manic ($p=0.002$ and 0.0001, respectively) and euthymic ($p=0.004$ and 0.002, respectively) bipolar I disorder subjects relative to healthy comparisons.
Limitations: The small sample sizes yield relatively low statistical power between manic and euthymic groups; cross-sectional observations limit the ability to determine if these findings are truly independent of mood state.
Conclusions: Our results suggest bioenergetic impairment – consistent with downregulation of creatine kinase – is an early pathophysiological feature of bipolar I disorder.

1. Introduction

Recent converging lines of evidence suggest that patients with bipolar disorder suffer from abnormalities in neuronal mitochondrial metabolism (Kato, 2006; Lee et al., 2012; Rezin et al., 2009; Stork and Renshaw, 2005). This hypothesis is supported by *in vivo* proton (^{1}H) and phosphorus (^{31}P) magnetic resonance spectroscopy (MRS) studies, as reviewed by Stork and Renshaw (2005). For example, findings of increased levels of lactate (Dager et al., 2004) and decreased intracellular pH (Hamakawa et al., 2004; Weber et al., 2013) in the prefrontal cortex of bipolar patients compared to healthy subjects suggests a shift toward glycolysis in response to impaired mitochondrial oxidative phosphorylation. In addition, using single voxel ^{31}P MRS, Kato et al. (1994) found decreases in phosphocreatine (PCr) levels in bipolar disorder. PCr serves as an energy reserve, becoming hydrolyzed to produce adenosine triphosphate (ATP) via an equilibrium mediated by the enzyme creatine kinase. Thus, decreases in PCr levels may suggest a decrease in total energy metabolism, consistent with mitochondrial dysfunction.

This suggestion is further supported by evidence of decreased levels of *N*-acetyl aspartate (NAA) in bipolar disorder (Stork and Renshaw, 2005). NAA is synthesized within mitochondria, and its synthesis correlates with ATP production and oxygen consumption (Petal and Clark, 1979). Decreases in NAA levels suggest a loss of available energy substrates. Furthermore our recent study showed that, compared to healthy subjects, adenosine diphosphate (ADP) concentration was significantly lower in the anterior cingulate cortex in manic subjects (Weber et al., 2013). It was suggested that [ADP] is more strongly correlated with mitochondrial function than [ATP] (Pan and Takahashi, 2005).

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Table 1
Subject information; Young Mania Rating Scale (YMRS) and Childhood Depression Rating Scale (CDRS) scores reported here were ascertained the day of scanning. Handedness was determined using the Crovitz–Zenner questionnaire.

Group	Sex	Age	YMRS	CDRS	Hand-edness	Tanner stage		Medication history (# weeks since last dose)
						Penis/breast	Pubic	
Control	F	13.3	0	17	Right	2	3	None
	F	12.7	0	18	Left	3	3	None
	F	16.4	2	18	Right	4	5	None
	F	15.3	0	17	Right	4	5	None
	F	16.4	4	18	Right	4	5	None
	F	15.5	4	19	Right	4	5	None
	F	13.3	2	19	Right	3	4	None
	F	16.7	1	18	Right	3	5	None
	F	12.9	0	17	Left	3	3	None
	F	13.7	0	17	Right	2	3	None
	M	13.8	0	17	Right	2	4	None
	M	16.8	5	19	Right	4	4	None
	M	12.0	1	17	Right	3	2	None
	M	12.4	1	17	Right	4	2	None
	M	16.8	0	17	Right	5	5	None
	M	17.4	1	19	Right	4	4	None
	M	16.0	4	18	Right	5	5	None
	M	21.4	1	17	Right	5	5	None
	M	19.7	0	17	Right	5	5	None
Euthymic	F	16.5	11	25	Right	5	4	Geodon (6), Abilify (10), Risperdal (17)
	F	17.1	4	23	Right	5	5	Geodon (30)
	F	16.8	12	24	Right	5	5	None
	F	17.5	5	26	Both	5	5	Depakote (21), Seroquel (21)
	F	13.8	12	28	Right	4	4	Vyvance (1), Abilify (2)
	F	17.6	8	26	Left	5	5	Seroquel (2), Risperdal (> 100)
	M	17.0	9	21	Right	5	5	Zoloft (22)
	M	17.9	7	21	Left	4	4	Seroquel (6), Topiramate (6)
Manic	F	17.2	21	47	Right	5	5	Lexapro (1)
	F	14.4	27	44	Both	4	4	None
	F	16.7	26	34	Right	5	5	Seroquel (2), Lexapro (2)
	F	15.2	29	54	Right	5	5	None
	F	16.5	21	33	Right	5	5	Olanzipine (2), Topiramate (1)
	F	17.2	28	33	Right	4	4	Abilify (2), Risperdal (11), Concerta (54)
	F	13.3	25	42	Both	4	4	Concerta (26)
	F	14.7	27	42	Right	4	4	Risperdal (> 52), Trileptal (> 52), Wellbutrin (> 52)
	M	16.8	22	33	Right	4	4	Focalin (1), Concerta (> 52)
	M	18.0	38	34	Right	4	4	Abilify (2)
	M	11.2	31	43	Right	3	3	Paxil (1 week), Adderall (3 months)
	M	17.2	24	40	Right	5	5	Zoloft (7), Risperdal (16)
	M	14.9	26	40	Right	4	4	Concerta (8), Zoloft (27)
	M	15.9	42	33	Right	5	4	None
	M	12.9	22	37	Right	3	2	Adderall (2), Risperdal (6), Focalin (> 250)
	M	14.8	32	53	Left	3	3	Risperdal (2), Citalopram (2), Lithium (30), Depakote (52), Seroquel (52)

Moreover, this model was strengthened by recent work that demonstrated significantly decreased expression of genes involved in mitochondrial function in bipolar patients compared with healthy subjects (Konradi et al., 2004). Postmortem studies have reported changes in mitochondrial-related gene expression in bipolar disorder (Iwamoto et al., 2005; Munakata et al., 2005; MacDonald et al., 2006). These studies further suggest that alterations in brain energy metabolism may be a critical index in the pathophysiology of bipolar disorder due to mutations in the mitochondrial genome (Kato and Kato, 2000).

Nonetheless, altered high energy metabolism as measured with single voxel ^{31}P MRS has produced inconsistent reports in bipolar disorder patients in several anatomical brain regions implicated in the pathophysiology of this illness. Several studies of bipolar patients found no differences in either PCr or ATP relative to healthy subjects (Kato et al., 1992; 1993; 1998; Deicken et al., 1995; Hamakawa et al., 2004; Sikoglu et al., 2013). Although discrepancies can be attributed to the differences of methodologies, mood state, and medication status among studies, another important confound – that is, the effect of brain tissue type – has recently been brought to our attention (Dudley et al., 2015). Therefore, in this work we aimed to eliminate this potential confound by applying tissue regression analysis to investigate the bioenergetic environments of homogenous gray and white matter in bipolar adolescent patients. This demographic provides a window of opportunity for clarifying early markers of disease progression with minimal confounding pharmacological effects. We hypothesized that tissue regression analysis would reveal that PCr will tend to be decreased in gray matter tissue but not white matter tissue of subjects with bipolar disorder relative to healthy comparisons.

2. Methods

2.1. Subjects

Participants with bipolar I disorder aged between 12 and 21 years were recruited from the University of Cincinnati Department of Psychiatry and the Cincinnati Children's Hospital Medical Center. A preliminary study involving this cohort has been previously reported (Weber et al., 2013). Demographically-matched healthy adolescents were recruited from the communities in which the bipolar participants resided. Diagnoses of bipolar I disorder were confirmed by trained raters with established diagnostic reliability