Journal of Affective Disorders 208 (2017) 139–144

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

1H-magnetic resonance spectroscopy study of glutamate-related abnormality in bipolar disorder

Hiroko Kubo[a], Masahito Nakataki[a,*], Satsuki Sumitani[a,b], Jun-ichi Iga[a,c], Shusuke Numata[a], Naomi Kameoka[a], Shin-ya Watanabe[a], Hidehiro Umehara[a], Makoto Kinoshita[a], Masatoshi Inoshita[a], Mai Tamaru[a], Masashi Ohta[a], Chiaki Nakayama-Yamauchi[d], Yasuhiro Funakoshi[d], Masafumi Harada[e], Tetsuro Ohmori[a]

[a] Department of Psychiatry, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan
[b] Department of Support for Students with Special Needs, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan
[c] Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Ehime, Japan
[d] Department of Medical Imaging, Institute of Biomedical Sciences, University of Tokushima Graduate School, Tokushima, Japan
[e] Department of Radiology and Radiation Oncology, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan

ARTICLE INFO

Keywords:
Bipolar disorder
Glutamate
Glutamine
Lithium
Sodium valproate
Magnetic resonance spectroscopy

ABSTRACT

Background: Previous studies of patients with bipolar disorder (BD) using magnetic resonance spectroscopy (MRS) have shown neurophysiological abnormalities related to the glutamate (Glu)-glutamine (Gln) cycle, membrane turnover, and neuronal integrity, although the results were neither consistent nor conclusive. Recently it has been reported the Gln/Glu ratio is the most useful index, quantifying neuronal-glial interactions and the balance of glutamatergic metabolites In this MRS study, we elucidated the abnormalities of metabolites in a larger sample of patients with BD with a high-field MRI system.

Methods: Sixty-two subjects (31 patients with BD and 31 healthy controls [HC]) underwent 3T proton MRS (1H-MRS) of the anterior cingulate cortex (ACC) and left basal ganglia (ltBG) using a stimulated echo acquisition mode (STEAM) sequence.

Results: After verifying the data quality, 20 patients with BD and 23 age- and gender-matched HCs were compared using repeated-measures analysis of covariance (ANCOVA). Compared to the HC group, the BD group showed increased levels of Gln, creatine (Cr), N-acetyl aspartate (NAA), choline (Cho), and an increased ratio of Gln to Glu in the ACC, and increased Gln and Cho in the ltBG. These findings remained after the participants with BD were limited to only euthymic patients. After removing the influence of lithium (Li) and sodium valproate (VPA), we observed activated glutamatergic neurotransmission in the ACC but not in the ltBG.

Limitations: The present findings are cross-sectional and metabolites were measured in only two regions.

Conclusions: Our results support a wide range of metabolite changes in patients with BD involved in glutamatergic neurotransmission, membrane turnover, and neuronal integrity. Moreover, the elevation of Gln/Glu ratio suggested that hyperactivity of glutamatergic neurotransmission in the ACC is a disease marker for BD.

1. Introduction

Bipolar disorder (BD) is characterized by recurrent episodes of depression and mania. It is a main cause of disability among young people, leading to cognitive and functional impairment and raised mortality, particularly death by suicide. Many studies have gradually elucidated the pathogenesis and pathophysiology of BD. Recently, glutamatergic neurotransmission in BD has been revealed by application of proton magnetic resonance spectroscopy (1H-MRS), which can noninvasively measure in vivo metabolite levels, including N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), glutamine (Gln), and glutamate (Glu), in specific brain regions. Glutamatergic neurotransmission can be assessed by measuring Gln, Glu, and Glx, which comprises Gln and Glu. Elevated Glx is one of the most replicated findings in BD (Taylor, 2014; Yüksel and Öngür, 2010). Gigante et al. (2012) conducted a systematic review of 9 articles including 162 BD subjects and reported that Glx levels were significantly elevated in several regions of the brain, even if the assessed area was limited to the

* Corresponding author.
E-mail address: nktk@tokushima-u.ac.jp (M. Nakataki).

http://dx.doi.org/10.1016/j.jad.2016.08.046
Received 1 June 2016; Received in revised form 11 July 2016; Accepted 23 August 2016
Available online 08 October 2016
0165-0327/

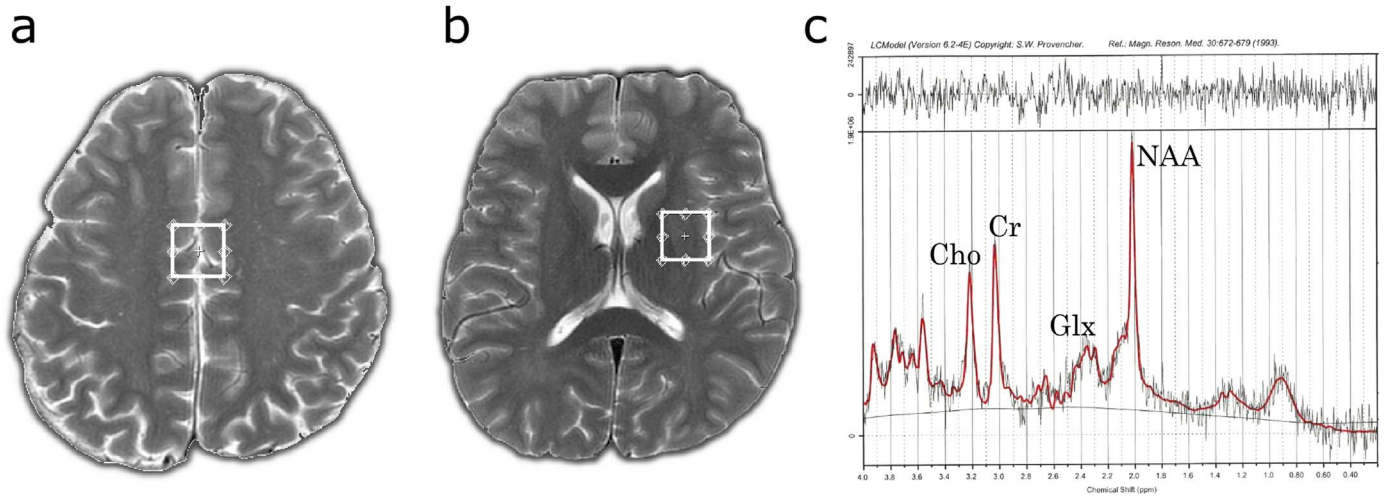

Fig. 1. Region of interest in (ROI) (a) the anterior cingulate cortex (ACC) and (b) the left basal ganglia (ltBG); (c) Sample magnetic resonance spectrum in LC Model. Abbreviations: Cho=Choline; Cr=creatine; Glx=Glutamate+Glutamine; NAA=N-acetyl aspartate.

frontal brain.

Most earlier 1H-MRS studies with 1.5 T scanners reported Glx (an overlapping resonance of Glu and its precursor Gln), whereas more recent studies, using 3 T scanners, can measure Glu and Gln separately. Gln is synthesized from Glu in astrocytes in a reaction catalyzed by Gln synthetase (GS) (Martinez-Hernandez et al., 1977). Synthesized Gln is transferred to presynaptic neurons and is the precursor for synaptic Glu; these process constitute the glutamine-glutamate cycle (Albrecht et al., 2010). The MRS signal of Glu and Gln represents more than just Glu and Gln at the synaptic cleft, however, because they play roles in intermediate metabolism. The Glu signal is dominated by the intracellular transmitter pool, and several measures indicate the use of Glu as a neurotransmitter (Erecińska and Silver, 1990). The Gln/Glu ratio is the most useful index, quantifying neuronal-glial interactions and the balance of glutamatergic metabolites. The Gln/Glu ratio increases and reductions may reflect increased and decreased glutamatergic neurotransmission (Hall et al., 2015). Several 1H-MRS studies reported abnormalities of Glu and Gln in patients with BD (reviewed by Yüksel and Öngür, 2010), whereas only five studies have reported Glu and Gln separately (Frye et al., 2007b; Kaufman et al., 2009; Moore et al., 2007; Ongür et al., 2008; Soeiro-de-Souza et al., 2015). Furthermore, only four reports have been published regarding the Gln/Glu ratio in patients with BD, three of which suggested elevated Gln/Glu in the anterior cingulate cortex (ACC) of patients with BD (Brennan et al., 2010; Ongür et al., 2008) and reduced Glu/Gln (Soeiro-de-Souza et al., 2015). Significant differences in glutamate concentration were reported between patients in depressive or manic episodes (Xu et al., 2013), however, whether glutamatergic neurotransmission is changed by mood-state shifts in BD is still unclear (Brady et al., 2014). The influence of medication on metabolite levels is also unclear (Brambilla et al., 2004; Friedman et al., 2004; Grošić et al., 2014; Machado-Vieira et al., 2015; Moore et al., 2000; O'Donnell et al., 2003; Shibuya-Tayoshi et al., 2008; Strawn et al., 2012; Szulc et al., 2013, 2011). It is thus difficult to interpret metabolite levels in MRS owing to the heterogeneity created by varying medication regimes.

In addition to the ACC, the basal ganglia (BG) are also highly involved in the pathophysiology of BD (Abler et al., 2008; Delvecchio et al., 2012; Hulvershorn et al., 2012; Hummer et al., 2013). However, published MRS studies of BD have reported varying results in the BG, indicating no significant change in Glx (Dager et al., 2004; Frye et al., 2007a; Kaufman et al., 2009), decreased Glx (Port et al., 2008), or elevated Glx (Castillo et al., 2000) with respect to levels in healthy controls.

In the present study, we investigated the hypothesis that metabolite abnormalities in the brain, particularly in the ACC and BG, would be present in patients with BD when compared to healthy controls.

2. Methods

2.1. Subjects

Thirty-one subjects with bipolar disorder and 31 control subjects participated in this study. The subjects were recruited from Tokushima University Hospital, Japan and signed written informed consent forms in accordance with the guidelines of the ethical committee at Tokushima University. The ethical committee approved this protocol. Subjects with BD were assessed using the DSM-IV TR (American Psychiatric Association, 2000). All patients were assessed using the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) and the Young Mania Rating Scale (YMRS; Young et al., 1978) on the scan day. Control subjects were assessed using the Zung Self-Rating Depression Scale (SDS) and had no history of an Axis I psychiatric illness as determined by the DSM-IV TR. All subjects were Japanese and none had a serious medical illness, neurodevelopmental disorder, or history of head injury, drug or alcohol abuse, or of taking hormonal drugs. All subjects were right-handed.

2.2. 1H-MRS procedure

1H-MRS was performed employing a 3 T magnetic resonance imaging (MRI) instrument (DISCOVERY MR750, GE, Milwaukee, USA) and a STEAM sequence with water suppression by CHESS pulses (TE=18 ms, TR=5000 ms, acquisition=64 times). Neurochemical compounds that can be identified in short-echo 1H-MRS include Cr, Glu, Gln, NAA, and Cho. The area under each of the magnetic resonances is proportional to the concentration of the particular compound. Metabolite levels were estimated using linear combination model (LCModel) software (Provencher, 1993). Our basis-set was constructed from original in vivo data for each metabolite. On the basis of previous reports of functional anomalies, the regions of interest (ROIs) for 1H-MRS were set as the anterior cingulate cortex and left basal ganglia, ROI size=6.0 ml, using three oriented images. For a reference slice of the ROI of the ACC, an axial cut was chosen ~1 cm above the upper end of the body of the lateral ventricles. The ROI was centered on the frontal interhemispheric fissure, 3 cm in front of the central fissure and 2 cm above the corpus callosum (Fig. 1a). A reference slice of the ltBG was placed between the Sylvian fissure and the lateral ventricles to encompass the lenticular nucleus (Fig. 1b). Representative 1H-MRS spectra of each compound in the ACC from one subject are shown in Fig. 1c.