Journal of Affective Disorders 150 (2013) 1238–1241

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Brief report

Risky alcohol use in young persons with emerging bipolar disorder is associated with increased oxidative stress

Kate M. Chitty *, Jim Lagopoulos, Ian B. Hickie, Daniel F. Hermens

Clinical Research Unit, Brain and Mind Research Institute, The University of Sydney, Sydney, NSW 2050, Australia

ARTICLE INFO

Article history:
Received 20 March 2013
Received in revised form
4 June 2013
Accepted 5 June 2013
Available online 6 July 2013

Keywords:
Glutathione
Anterior cingulate cortex
Proton magnetic resonance spectroscopy
Bipolar disorder
Alcohol

ABSTRACT

Background: Alcohol misuse is highly prevalent in bipolar disorder (BD) and has been associated with increased formation of reactive oxygen species in the CNS. Proton magnetic resonance spectroscopy (^{1}H-MRS) is an in vivo tissue-based imaging modality that allows the investigation of changes in the brains primary antioxidant, glutathione (GSH), as a result of alcohol use in this population.
Methods: Thirty-three patients with BD and 17 controls aged 18–30 years were recruited. Participants completed the Alcohol Use Disorders Identification Test (AUDIT) and underwent ^{1}H-MRS. Levels of GSH in the anterior cingulate cortex (ACC) were determined. ANOVA was conducted to determine differences between high and low risk drinking bipolar participants and controls.
Results: ANOVA with all groups revealed a significant difference in GSH between bipolar high and low risk drinkers, with those in the high-risk group displaying reduced GSH levels. A significant negative correlation was found between total AUDIT score and GSH in bipolar ($R=-0.478$, $p=0.005$) which remained significant when controlling for age and medication status.
Limitations: Our participant sample consisted of a heterogeneous group of patients, most of whom were medicated at time of testing.
Conclusions: Young people with emerging BD who drink at risky levels display reduced levels of ACC-GSH. Increased oxidative stress and its resulting neurotoxic effects may be especially detrimental in an emerging bipolar sample where the illness trajectory is unclear and the brain is still undergoing significant development.

1. Introduction

Alcohol misuse is highly prevalent in bipolar disorder (BD), with rates of up to 69.9% of lifetime misuse reported in youth with the condition (Cassidy et al., 2001). A recent study identified 20–30 years old males with BD as one of the most likely groups in a young psychiatric cohort to participate in weekly substance use (Hermens et al., 2013). Alcohol misuse and dependence in BD has been associated with a significant negative impact on illness progression (Frye and Salloum, 2006) though a recent review has indicated that while alcohol use disorders (AUD) are associated with rapid cycling and mood episode switching, its effects on bipolar course remain unknown (Rakofsky and Dunlop, 2013). Given the wide spectrum of symptomology expressed by individuals with BD identifying whether alcohol is a potential risk factor for the development of mania or rapid cycling is imperative. Proton magnetic resonance spectroscopy (^{1}H-MRS) is an in vivo tissue-based imaging modality that presents an opportunity to investigate changes in neurochemistry resultant from alcohol use.

Examining neurochemistry associated with oxidative stress is an area of interest given ethanol's demonstrated propensity to stimulate the formation of reactive oxygen species (ROS), which in turn depletes antioxidant defences in the brain (Nordmann et al., 1990). Neural tissue is especially prone to oxidisation due to its high content of oxygen and easily oxidisable substrates, paired with its relatively low activity of antioxidant defence molecules. Oxidative stress has been hypothesised as the biochemical link between alcohol consumption and its effects on the brain (Nordmann et al., 1990). Accordingly, levels of the brains most potent antioxidant, glutathione (GSH), are decreased after ethanol treatment in rats (Agar et al., 1999; Reyes et al., 1993; Uysal et al., 1989).

Models of oxidative stress have also been described as potential pathophysiological processes associated with BD (Andreazza et al., 2008; Berk et al., 2011). A recent ^{1}H-MRS study found no difference in the levels of in vivo GSH between controls and people with BD (Lagopoulos et al., 2013), however given the evidence that alcohol use is associated with increased oxidative stress, we sought to investigate whether GSH is compromised in patients

* Correspondence to: Brain & Mind Research Institute, University of Sydney. Tel.: +61 2 9351 0724; fax: +61 2 9351 0652.
E-mail address: kate.chitty@sydney.edu.au (K.M. Chitty).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.06.003

who drink. The Alcohol Use Disorder Identification Test (AUDIT) is a useful instrument for detecting alcohol use in patients with mental health issues, including BD (Reinert and Allen, 2007). The purpose of this study was to assess the effects of alcohol use on GSH, in young patients with BD.

2. Methods

2.1. Participants

Thirty-three patients with BD (18–30 years) were recruited from a specialized tertiary referral service (Scott et al., 2012). Diagnoses were determined by a psychiatrist using DSM-IV criteria confirming diagnoses of bipolar II ($n=24$) or bipolar spectrum with family history of BD ($n=9$), defined as an illness pattern consisting of periods of both elevated and depressed mood consistent with a bipolar spectrum disorder (Angst, 2007).

Patients' normal psychotropic medication regimens were not interrupted in any way. At the time of testing eight (24.2%) of patients were medication free, 17 (51.5%) were taking anti-depressants, 16 (48.5%) were taking atypical antipsychotics, 10 (30.3%) were taking mood stabilizers. Two patients were taking benzodiazepines.

Seventeen controls (20–29 years) were recruited from the community. Exclusion criteria for all participants were medical instability, history of neurological disease, medical illness known to impact cognitive and brain function, intellectual disability and insufficient English for assessment. Controls were excluded if they reported risky levels of alcohol use as determined by the AUDIT. Participants were asked to abstain from illicit drug or alcohol use for 48 h before testing.

The study was approved by the University of Sydney ethics committee. Participants gave written informed consent before participation.

2.2. Self-report measures

All participants completed the AUDIT in self-report format. We used the sex-specific cut-off scores for detecting risky alcohol use in psychosis (as it has not yet been established specifically in BD); a total AUDIT score of 10 or more out of 40 for men and eight for women (Nesvag et al., 2010). The bipolar group was then split into low-risk drinkers (BD-low) and high-risk drinkers (BD-high) according to these cut-offs.

Current symptoms were assessed using the depression anxiety stress scale (DASS; (Lovibond and Lovibond, 1995)) and the Kessler-10, a psychological distress scale (Kessler et al., 2002).

2.3. ^{1}H-MRS data acquisition and processing

As per our protocol (Hermens et al., 2012, Lagopoulos et al., 2013), participants were scanned on a 3Tesla GE Discovery MR750 MRI (GE Medical Systems, Milwaukee, WI). First, a 3D sagittal whole-brain scout was undertaken for orientation and positioning of scans (TR=50 ms; TE=4 ms; 256matrix; no averaging, $z=5$ mm thickness). Next a T1-weighted Magnetization Prepared RApid Gradient-Echo (MPRAGE) sequence producing 196 sagittal slices (TR=7.2 ms; TE=2.8 ms; flip angle=10°; matrix 256×256; 0.9 mm isotropic voxels) was acquired for the purpose of localization of the anterior cingulate cortex (ACC). Finally, a $2\times2\times2$ cm single voxel was then placed midline on the ACC (Fig. 1A) and spectroscopy data was acquired using PRESS (TE=35 ms, TR=2000 ms, 128 averages) along with two chemical shift-selective imaging pulses for water suppression. All spectra were shimmed to achieve full-width half maximum (FWHM) of <13 Hz and visually inspected by independent raters. Data with Cramer–Rao Lower Bound greater than 20% were excluded. To obtain reference spectra used to determine GSH quantification, six phantom solutions containing varying concentrations of GSH (0–7.0 mM) were prepared with physiological brain concentrations of creatine, glutamate and glutamine in a phosphate buffer. All solutions were kept at 37 °C, and GSH linear dependence was calculated as $R^2=0.994$.

Data were transferred offline for post processing using the LCModel software package (Provencher, 1993). All spectra were quantified using a GAMMA-simulated PRESS TE 35 basis set of 15 metabolites (including GSH) and incorporated macromolecule and baseline fitting routines (for spectra see Fig. 1A). Absolute GSH concentration was determined using the ensuing reference spectral calibration curve. Following this, the coordinates of the acquired ACC voxels for each participant were obtained using the SAGE (Spectroscopy Analysis GE) software package and the reconstructed acquisition voxels for all participants were corrected for grey matter (GM) content.

GM correction was achieved by segmenting each participant's structural image into GM, white matter (WM) and CSF using the FAST4 algorithm as implemented in FSL (Zhang et al., 2001) and volume fractions were calculated. All subsequent statistical analyses were conducted on GM-corrected absolute GSH concentration.

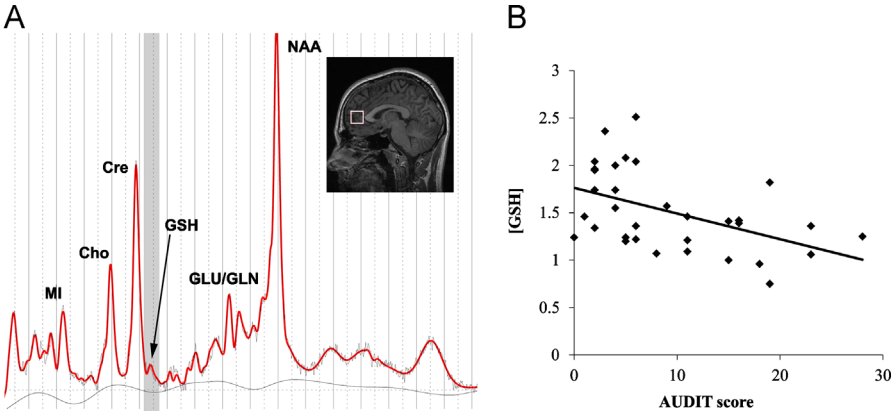

Fig. 1. (A) Water suppressed GSH spectra (sampled from the ACC) processed using LCModel. The GSH metabolite peak is resolved at 2.95 ppm. The insert shows a sagittal view of a representative T1-weighted image illustrating the acquisition voxel size and placement for the ACC. (B) Scatterplot of absolute GSH (I.U.) in grey matter of ACC voxel against total AUDIT score of bipolar spectrum patients ($n=33$). (ACC, anterior cingulate cortex; AUDIT, alcohol use disorders identification test; Cho, choline; Cr, creatine; GLX, glutamine fl glutamate; GSH, glutathione; MI, myo-inositol; NAA, *N*-acetyl aspartate).