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Medial temporal lobe glutathione concentration in first episode psychosis: A ^{1}H-MRS investigation

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ABSTRACT

Glutathione (GSH) is implicated in the pathophysiology of schizophrenia. Previous brain spectroscopy studies, however, have been inconsistent, and there is little data available from first episode psychosis patients. This study compared brain GSH in a first episode cohort ($n=30$) to controls ($n=18$), using magnetic resonance spectroscopy (MRS), examining a temporal lobe voxel. Short-echo (TE 30 ms) acquisition proton MRS was performed on a 3T clinical magnetic resonance scanner. Comparison of the first-episode and control groups' GSH concentrations revealed a significant main effect of group ($F_{1,46}=4.7$, $p=0.035$), but no main effect of hemisphere ($F_{1,46}=2.3$, $p=0.137$) or group-by-side interactions ($F_{1,46}=0.4$, $p=0.513$). Medial temporal lobe GSH concentrations in the first episode group were 22% higher than those in the control group. This study provides further evidence of significant perturbations in brain GSH in first episode psychosis, and supports a broader involvement of GSH in the pathophysiology of schizophrenia.

Introduction

The brain generates a high load of reactive oxygen species, and this burden is increased by factors including the oxidative potential of excitatory neurotransmitters and the vulnerability of the brain's lipid components to oxidation (Yao et al., 2001). Oxidative stress has been associated with psychiatric disorders such as schizophrenia (Berk, 2007; Ng et al., 2008), and although *in vivo* measurement of free radical concentrations is impractical because of their short half-lives and low levels, oxidative status can be assessed by measuring plasma lipid peroxides (Khan et al., 2002). These are found at higher concentration in schizophrenia, and correlate positively with symptom severity (Arvindakshan et al., 2003), and inversely with membrane levels of essential polyunsaturated fatty acids levels (Reddy et al., 2004).

Glutathione (GSH) is the brain's dominant antioxidant and also implicated in the pathophysiology of schizophrenia. There is a 27% reduction in the cerebrospinal fluid levels of GSH in untreated patients (Do et al., 2000), and a similar reduction (41%) in the caudate post-mortem (Yao et al., 2006). Further, increased risk of schizophrenia is associated with polymorphisms of genes associated with GSH synthesis (Saadat et al., 2007; Tosic et al., 2006).

An alternative approach to measuring glutathione is proton magnetic resonance spectroscopy (^{1}H-MRS), which allows *in vivo* measurement in larger and more representative populations across illness stages. To date there are three such studies, all of which obtained spectra from a mid-sagittal voxel in the prefrontal cortex. In the first (Do et al., 2000), 14 patients were compared to 10 controls, and the patient group showed a roughly 50% reduction in glutathione. In the second (Terpstra et al., 2005), 13 patients were compared to 9 controls, but no significant differences were found (roughly a 6% reduction in the patient group). Similar findings were reported by the third study (Matsuzawa et al., 2008; 20 patients, 16 controls, non-significant 13% reduction). One plausible reason for these differences is medication—all patients were medicated in the latter two studies, only five in the first—but the evidence for such an effect is weak (Martins et al., 2008).

All but one of the patients reported in these previous MRS studies had established illness, and all had onset of symptoms at least 8 months before scanning. First episode patients with shorter illness duration may not show differences in GSH concentration, since they tend to show less consistent neurobiological abnormalities compared to established schizophrenia cases (e.g. Velakoulis et al., 2006).

In this study we examined ^{1}H-MRS measures of glutathione in the medial temporal lobes of 30 first episode psychosis patients. The medial temporal lobes were selected because of their known

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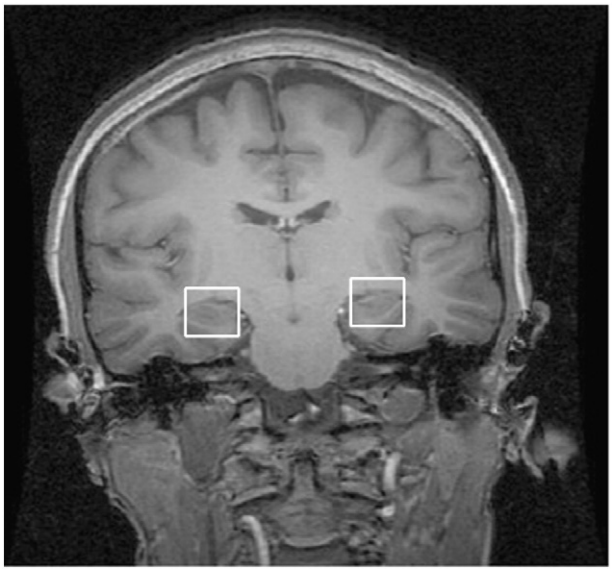

Fig. 1. MR image showing placement of the two medial temporal voxels for acquisition of spectra.

involvement in schizophrenia (e.g. Velakoulis et al., 2006) and vulnerability to insult. In addition, we indirectly measured oxidative stress by recording the skin flush response to topical niacin (Smesny et al., 2003, 2004). We predicted that there would be a reduction in GSH concentration in first-episode psychosis, and that this would be greater in those who failed to show the normal skin response to niacin.

Materials and methods

Participants

Thirty patients who were part of a larger randomized double-blind placebo-controlled clinical trial (Berger et al., 2007) were recruited from the Early Psychosis Prevention and Intervention Centre at ORYGEN Youth Health. Study inclusion criteria were: (1) age at onset 15–29 years (inclusive), (2) currently psychotic as reflected by the presence of at least one of; (a) delusions, (b) hallucinations, (c) disorder of thinking/speech, other than simple acceleration or retardation, (d) disorganised, bizarre, or markedly inappropriate behaviour. DSM-IV diagnoses were obtained from all patients using the Structured Clinical Interview for DSM-IV (First et al., 1997). Diagnoses were schizophrenia (n=9), schizophreniform psychosis (n=11), schizoaffective disorder (n=3), major depression with psychotic symptoms (n=4) and psychosis NOS (n=3). Patients with a diagnosis of bipolar disorder with psychotic features were not recruited but referred to a concurrent intervention study running onsite. Thirteen patients were scanned neuroleptic-naïve, while the remaining 17 had received at least one dose of an atypical antipsychotic medication (risperidone n=8, quetiapine n=5, and olanzapine n=4; median number of days of treatment=6; median cumulative dose at scan (chlorpromazine equivalents)=600 mg, range 101–4600 mg). Eighteen healthy volunteers were selected from a larger sample, recruited from similar socio-demographic areas as the patients, in order to match as closely as possible for age and gender.

All subjects were screened for co-morbid medical and psychiatric conditions by clinical assessment, physical and neurological examinations. Exclusion criteria for all subjects were: a history of significant head injury, seizures, neurological diseases, current substance dependence, impaired thyroid function or steroid use, but not a history of substance dependence. Control subjects with a personal history of psychiatric illness or family history of psychosis were excluded. The local research and ethics committee approved this protocol, and each subject (or their guardian) provided written informed consent.

Proton magnetic resonance spectroscopy

Short-echo (TE 30 ms) acquisition proton MRS was performed on a 3T GE LX Horizon scanner (GE Healthcare, Milwaukee, USA) using a standard PRESS sequence incorporating two chemical-shift selective imaging pulses for water suppression and third-order shims. Spectra were acquired with 128 transients of 2k data points over a frequency width of 5000 Hz with a repetition time (TR) of 3 s. Spectra were recorded from single isotropic 2 cm voxels, placed in each temporal lobe. Three-plane localizing images were acquired to allow prescription of regions of interest (ROI) for spectra. A ROI in each temporal lobe was selected in the coronal plane with the lateral aspect of the hippocampus in the centre of the ROI (Fig. 1). The sagittal image was viewed to ensure that the ROI did not include petrous temporal bone. This ROI consisted largely of the anterior hippocampus (>50%). Spectra were analyzed with LCModel (Provencher, 1993), using a basis set of 15 metabolites acquired on-site, using standard macromolecule and baseline fitting routines that incorporate adjustments for broad macromolecular components (results for metabolites other than glutathione have been published previously in Wood et al., 2008). The advantage of this approach is that the broad components are not tied to specific macromolecules. Glutathione concentrations were estimated using the tissue water signal as an internal standard (see Fig. 2). Although peaks from other metabolites overlap with the glutathione spectrum, it is possible to detect the glutathione contribution even when all individual metabolite peaks are not clearly visible (Pfeuffer et al., 1999a,b). Comparisons of a short-echo single voxel acquisition method, as used in this study, with spectral editing techniques for glutathione measurement showed that the method used in our study gives comparable results (Oz et al., 2006; Terpstra et al., 2005). Results are presented in institutional units approximating millimolar concentration and were rejected if the Cramer-Rao lower-bound was greater than 50% (mean left=20.1±7.8; mean right=22.0±8.5). Full-width-half-maxima (to the water peak) and signal-to-noise ratios averaged 11.6±2.2 Hz and 11.4±2.3, respectively, across both hemispheres.

Topical niacin skin-flush test

Niacin (Highland Psychiatric Research Foundation) was applied simultaneously in four dilutions (0.1, 0.01, 0.001, and 0.0001 M) of

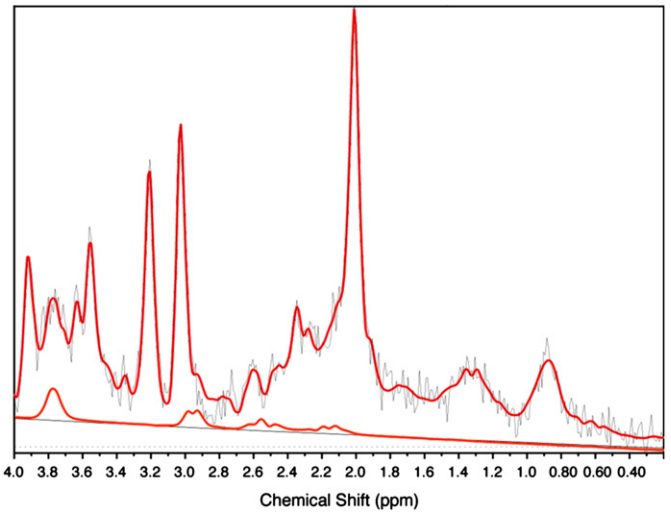

Fig. 2. Example LCModel output showing both the overall fit and the specific quantification for glutathione.