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Taurine and glutathione in plasma and cerebrospinal fluid in olanzapine treated patients with schizophrenia

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ABSTRACT

Oxidative stress has been implicated in the pathophysiology of schizophrenia. Taurine and glutathione (GSH) have antioxidant and central nervous system protective properties, and are proposed to be involved in the pathology of schizophrenia. The aim of this study was to compare the blood and cerebrospinal fluid (CSF) levels of taurine and GSH in patients with schizophrenia, medicated with oral olanzapine, compared with controls. In total, 37 patients with schizophrenia and 45 healthy volunteers were recruited. We found the plasma taurine levels to be elevated in patients compared with controls. No differences were, however, found between patients and controls regarding taurine in CSF or GSH concentrations in plasma and CSF. Moreover, in the patient group no correlations between taurine and GSH levels and the symptoms or function of the disorder were found. The higher levels of plasma but not CSF taurine in patients with schizophrenia treated with OLA may implicate the involvement of taurine in the pathophysiology of the disease. The absence of GSH differences both in plasma and CSF between patients and controls is interesting in the perspective of earlier research proposing a dysregulation of GSH metabolism as a vulnerability factor for the development of schizophrenia.

1. Introduction

Schizophrenia is a devastating lifelong disorder affecting approximately 0.5% of the world's population. Currently, the underlying pathophysiological mechanisms of the disorder are largely unknown (Sadock et al., 2009). An imbalance in the antioxidant defence system due to persistent oxidative stress has been described, and oxidative damage has been implicated in the pathology of schizophrenia (Do et al., 2009; Bitanihirwe and Woo, 2011; Yao and Reddy, 2011). Recent findings have pointed out the sulphur-containing compounds glutathione (GSH) and taurine as important regulators of the redox balance and the response to inflammatory processes (Schuller-Levis and Park, 2003; Haddad and Harb, 2005), which imply importance in schizophrenia.

Like GSH, taurine uses cysteine for its biosynthesis and is one of the most abundant free amino acid derivatives in the body (Schuller-Levis and Park, 2003). In addition to its antioxidant properties, taurine acts as a neuroprotector and neuromodulator and is important for the development and regeneration of the central nervous system (CNS) (Huxtable, 1992; Wu et al., 2005). In patients with schizophrenia, a pathophysiological role of taurine has been suggested, as the level is reported to be increased in the brain prefrontal cortex, and this rise is correlated with illness duration (Shirayama et al., 2010). In animal models of intrauterine infections, a decrease in hippocampal taurine levels of the foetus has been shown, supporting the causal relationship between maternal infection/inflammation during pregnancy and a higher risk for schizophrenia-related neuropathology in the adult offspring (Winter et al., 2009). In addition, altered taurine levels have been documented in patients with acute polymorphic psychosis and depression and in pathological gamblers (Fekkes et al., 1994; Nordin and Sjödin, 2006; Samuelsson et al., 2012).

GSH is the major intracellular nonprotein thiol protecting against oxidative damage and harmful xenobiotics. In the brain, it is also involved in neurotransmission and neuromodulation (Dringen, 2000), and deficiency or depletion of GSH in the brain has been implicated in several pathological conditions in which oxidative stress is important (Ristoff and Larsson, 2007). A deficit of blood GSH during first-episode psychosis has been found in drug naïve patients (Raffa et al., 2011) and is associated with the loss of brain cortical grey matter (Fraguas et al., 2012). Several studies have shown associations between genes coding for

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GSH-related enzymes and schizophrenia (Tosic et al., 2006; Gysin et al., 2007; Gravina et al., 2011; Nafissi et al., 2011). In rodent models behavioural, morphological, electrophysiological and neurochemical alternations, which resembles pathologies seen in patients with schizophrenia could be coupled to GSH deficiency (Kulak et al., 2013).

Olanzapine (OLA) is an atypical antipsychotic drug prescribed for the treatment of schizophrenia and schizoaffective and bipolar syndromes (Sadock et al., 2009). OLA is efficient against positive and negative symptoms of schizophrenia (Bymaster et al., 1999), and there are indications that it has one of the most favourable pharmacological protective profiles compared with other antipsychotic drugs (Wei et al., 2003; Pillai et al., 2007; Sadock et al., 2009). However, the potential risk of developing metabolic syndrome has been found in some patients treated with OLA (Stahl, 2008; Sadock et al., 2009).

Modulation of taurine and GSH levels has been investigated as pharmacological strategies in schizophrenia. The taurine analogue acamprosate has been proposed to offer a better pharmacological profile in early stages of schizophrenia compared with risperidone and OLA (Paz et al., 2008). Orally administered N-acetyl cysteine (NAC), which is a precursor of GSH, is a possible way to reduce the oxidative burden in patients with schizophrenia (Ng et al., 2008; Bošković et al., 2011; Reddy and Reddy, 2011). In a randomized double-blind, placebo-controlled study, NAC administration was found to give moderate improvement of chronic schizophrenia (Berk et al., 2008). In addition Carmeli et al. (2012) found that NAC administration resulted in significant changes in EEG synchronisation and these changes may precede clinical improvement in patients with schizophrenia. Because taurine also depends on cysteine for its biosynthesis, it is likely that taurine levels could also be modified by NAC (Schuller-Levis and Park, 2003).

Studies, in both blood and CSF, indicate that taurine and GSH levels are altered in patients with schizophrenia compared to healthy individuals (Bjerkenstedt et al., 1985; Rao et al., 1990; Do et al., 1995, 2000; Raffa et al., 2009). In previous studies, we found complex associations between the taurine (Samuelsson et al., 2009) and GSH (Samuelsson et al. 2011) levels in plasma and CSF in healthy men. The aim of the present study was to further explore GSH and taurine levels in CSF and blood and to correlate to symptoms and the level of function in outpatients with schizophrenia medicated with oral OLA compared with healthy controls.

2. Methods

2.1. Patients

Fifty-four Caucasian outpatients diagnosed with schizophrenia or schizoaffective disorder according to DSM-IV (American Psychiatric Association, 1994) criteria were identified and screened for inclusion. All of the patients were prescribed OLA as the only antipsychotic drug. No patient was a first-episode patient, and all but three had received prior treatment with antipsychotic drugs other than OLA. The patients had been on medication with OLA for between 0.2 and 11 years (median 2 years) and had been on the same dose of OLA (2.5–25 mg/day) for at least 14 days. Concomitant drugs were benzodiazepines and/or zopiclone in 10 patients and lithium in three. Only somatically healthy patients, as judged by routine laboratory analyses (electrolytes, blood, kidney, liver and thyroid measurements) and physical examination, were eligible. Of the 54 patients, 37 (schizophrenia $n=31$ and schizoaffective disorder $n=6$) were found to be eligible and agreed to participate. Seventeen patients either refused to take further part in the study or did not fulfil the inclusion criteria. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gordham, 1962) and Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994) index were used to evaluate the symptoms and level of function, respectively. Plasma was collected from all patients ($n=37$), and CSF was successfully collected from 24.

2.2. Controls

As controls, 45 healthy Caucasian volunteers (30 males and 15 females in the follicular phase of the menstrual cycle) were recruited, as previously described (Samuelsson et al., 2009; Lundberg et al., 2010). All of the CSF samples were analysed for taurine, but due to too low volume, four GSH samples were excluded; thus, 41 CSF samples were analysed for GSH. All of the plasma samples were analysed for taurine, but due to collecting errors, only 40 were analysed for GSH. The clinical characteristics of patients and controls are shown in Table 1.

Table 1
Demographic and clinical characterisation of 37 patients (25 males and 12 females) and 45 controls (30 males and 15 females).

	Population	Controls	Patients	P	t	d.f.
Age[a] (years)	All	25 (18–51)	37 (23–49)	<0.0010	-8.20	80
	Men	25 (18–51)	36 (23–49)	<0.0010	-5.56	53
	Women	24 (19–32)	38 (26–47)	<0.0010	-7.02	25
BMI[b]	All	24.0 ± 2.9	26.1 ± 4.2	<0.010	-2.67	80
	Men	23.9 ± 2.9	26.1 ± 4.5	0.033	-2.18	53
	Women	24.2 ± 2.9	26.1 ± 3.7	0.15	-1.50	25

[a] Mean age, range within brackets.
[b] BMI=body mass index (mean ± S.D.).

2.3. Ethical considerations

The patients and controls were recruited at Linköping University Hospital, and the study was conducted at the Department of Clinical and Experimental Medicine, Division of Psychiatry, Linkoping University, Sweden. The study was approved by the Ethics Committee of Linköping University and the Swedish Medical Products Agency. All of the volunteers and patients received verbal and written information and gave their written informed consent. The study adhered to principles embodied in the Declaration of Helsinki (Rickham, 1964).

2.4. Plasma and CSF sampling

Samplings of blood and CSF were performed in the morning at 8:00 a.m. after a minimum of 8 h in the fasting state, with no restrictions concerning posture or rest. Fasting blood samples were collected in heparinised tubes and centrifuged at 1438 *g* for 10 min (Sigma 203 centrifuge). Plasma was separated and stored at −70 °C until analysis. For lumbar puncture, a disposable needle (BD Whitacre Needle 0.7 × 90 mm) was inserted at the L 4-5 level with the subject in the right decubitus position. CSF was allowed to drip into a plastic test-tube. The CSF samples were protected from light, centrifuged at 1438 *g* for 10 min (Sigma 203 centrifuge) within 30 min after the puncture, and divided into 2- to 3-ml aliquots. Samples were stored at −70 °C pending analysis. Due to the disrupted gradient for GSH (Samuelsson et al., 2011), the second CSF fraction (7–12 ml) was used for both analyses.

2.5. Laboratory analysis

Taurine was analysed by high-performance liquid chromatography in a Biochrom 30 Amino Acid Analyser with spectrophotometrical detection. The EZ Chrom Elite programme was used for the final calculation of concentrations (Jeppsson and Karlsson, 1972; Ekberg et al., 1974; Brattström et al., 1988). The total amount of glutathione (reduced and oxidised) was analysed spectrophotometrically by the reduction of 5,5′-dithiobis-2-nitrobenzoic acid (Akerboom and Sies, 1981), as previously described (Samuelsson et al., 2011). OLA and its active metabolite N-demethylolanzapine (DMO) were analysed by liquid chromatography/tandem mass spectrometry as previously described (Skogh et al., 2011).

2.6. Statistical analysis

Kolmogorov–Smirnov and Lilliefors tests were used to verify normal distribution, and parametric statistics were used for normally distributed data. Student's *t*-test for independent variables (by group) and Pearson's correlation analysis were used for analysis of the data. *P*-values below 0.050 were considered to be significant. The Statistica 8 program was used.

3. Results

Plasma taurine levels were found to be elevated in patients compared with controls ($t=-5.04$, d.f.=80, $P=0.000003$; females $t=-5.90$, d.f.=25, $p<0.00001$; and males $t=-2.45$, d.f.=53, $P<0.050$). In the control group, females had lower plasma taurine levels compared with male controls ($t=3.80$, d.f.=43, $P<0.0010$), but in the patient group, no statistical differences were found