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Increased breath ethane levels in medicated patients with schizophrenia and bipolar disorder are unrelated to erythrocyte omega-3 fatty acid abundance

Brian M. Ross [a], Ross Maxwell [b], Iain Glen [b,*]

[a] Northern Ontario School of Medicine, Lakehead University, Thunder Bay, Ontario, Canada
[b] University of the Highlands and Islands, Inverness, Scotland, UK

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ABSTRACT

Oxidative stress has been reported to be elevated in mental illness. Preliminary evidence suggests this phenomenon can be assessed non-invasively by determining breath levels of the omega-3 polyunsaturated fatty acid (PUFA) oxidation product ethane. This study compares alkane levels in chronic, medicated, patients with schizophrenia or bipolar disorder with those in healthy controls. Both ethane and butane levels were significantly increased in patients with schizophrenia or bipolar disorder, although elevated butane levels were likely due to increased ambient gas concentrations. Ethane levels were not correlated with symptom severity or with erythrocyte omega-3 PUFA levels. Our results support the hypothesis that oxidative stress is elevated in patients with schizophrenia and bipolar disorder leading to increased breath ethane abundance. This does not appear to be caused by increased abundance of omega-3 PUFA, but rather is likely due to enhanced oxidative damage of these lipids. As such, breath hydrocarbon analysis may represent a simple, non-invasive means to monitor the metabolic processes occurring in these disorders.

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1. Introduction

Schizophrenia and bipolar disorder are both common and serious mental illnesses which possess high morbidity and mortality, with significant numbers of persons with these disorders committing suicide (Müller-Oerlinghausen et al., 2002; Mueser and McGurk, 2004). Schizophrenia, which effects approximately 1% of the population, normally presents in adolescence or early adulthood with a combination of so-called positive symptoms e.g. delusions, hallucinations, and negative symptoms such as avolition and anhedonia (Mueser and McGurk, 2004). Bipolar disorder has a higher population prevalence of 1.5%, and is considered to be a disorder of mood. It is characterised by cyclical mood swings from mania to depression, with periods of normal mood termed the euthymic state (Müller-Oerlinghausen et al., 2002). The two disorders, from a behavioural standpoint, are therefore considered distinct and are listed as such in the Diagnostic and Statistical Manual which describes the various forms of mental illness (American Psychiatric Association, 1994). Many patients, however, do not fit well into each definition, displaying symptoms which combine aspects of each illness, such as bipolar disorder with psychosis and schizoaffective disorder (Ketter et al., 2004), although differences in the development and treatment of bipolar disorder and schizophrenia remain (Murray et al., 2004). Moreover, a person who has a relative with schizophrenia is more likely to develop bipolar disorder and vice versa (reviewed by Berrettini, 2003). These observations strongly suggest that the two disorders possess certain common pathophysiological mechanisms (Murray et al., 2004). A candidate mechanism is that of chronic oxidative stress.

Oxidative stress describes the reaction between cellular molecules, such as DNA, lipids and proteins, and free radicals (highly reactive molecules characterised by unpaired electrons) generated during normal oxidative metabolism (Halliwell and Gutteridge, 1999). The vast majority of these reactions modify the function of the molecule in a detrimental manner, the cumulative effect of which is to disrupt cellular function ultimately leading to cell death (Halliwell and Gutteridge, 1999). To reduce the rate of oxidative damage, cells possess several defence mechanisms which act to detoxify the oxidising free radicals, these being termed anti-oxidants. These include enzymes such as catalase, superoxide dismutase and glutathione peroxidise. In addition, antioxidant compounds, such as vitamin E which react with free radicals and thereby preserve other cellular constituents (Halliwell and Gutteridge, 1999). As such the degree of oxidative stress a cell experiences is determined by the balance between oxidative and anti-oxidative factors.

Abbreviations: BD, bipolar disorder; SCZ, schizophrenia; PUFA, polyunsaturated fatty acid; DSM, diagnostic and statistical manual; BPRS, brief psychiatric rating scale; PANSS, positive and negative symptom scale; CGI, clinical global impression; HDRS, Hamilton depression rating scale; YMRS, Young mania rating scale; ATD, automatic thermal desorption; GCMS, gas chromatography mass spectroscopy; EDTA, ethylenediaminetetraacetic acid; ANOVA, analysis of variance; ANCOVA, analysis of covariance; CPZ, cholpromazine.

* Corresponding author. University of the Highlands and Islands, 12b Ness Walk, Inverness, United Kingdom, IV3 5SQ. Tel.: +44 1463 279000.
E-mail address: iainglen@dalnavert.sol.co.uk (I. Glen).

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Much evidence suggests that oxidative stress is elevated in schizophrenia including in the early 'first-break' stage of the illness (Reddy et al., 1991; Mahadik and Mukherjee, 1996; Akyol et al., 2002). This conclusion relies mainly on measurements of specific components of the anti-oxidant systems (for example see Mukerjee et al., 1996; Yao et al., 1998, 1999; Herken et al., 2001; Akyol et al., 2002; Kuloglu et al., 2002; Evans et al., 2003; Ranjekar et al., 2003), by detecting the abundance of oxidation products of DNA, protein, or lipids (Nishioka and Arnold, 2004; Young et al., 2007; Dietrich-Muszalska and Olas, 2007; Dietrich-Muszalska et al., 2009; Wang et al., 2009), or by detecting loss of oxidation-sensitive polyunsaturated fatty acids (PUFA) (e.g. see Yao et al., 1994; Khan et al., 2002; Arvindakshan et al., 2003; Evans et al., 2003) given that measurement of the reactive and short-lived free radicals themselves is extremely difficult. Furthermore, when the system is considered as a whole, a consistent abnormality emerges, indicating an overall elevated susceptibility to free radical damage in schizophrenia (Yao et al., 1998; Ustundag et al., 2006; Virit et al., 2009). The investigation of oxidative stress in bipolar disorder has been less extensive than that for schizophrenia, however similar findings to that observed in patients with schizophrenia have been reported including abnormal anti-oxidant enzyme activities, total anti-oxidant activity, a greater abundance of oxidation products, and reduced levels of PUFA (Chiu et al., 2003; Ranjekar et al., 2003; Savas et al., 2006; Machado-Vieira et al., 2007; Andreazza et al., 2007a, 2007b, 2009; Frey et al., 2007; Yumru et al., 2009; Wang et al., 2009). Indeed, mitochondrial dysfunction leading to oxidative stress has been implicated in both disorders (reviewed in Rezin et al., 2009). The functional consequences of increased oxidative stress, studied using animal models of the phenomenon, has indicated increased oxidation negatively affects brain development and function, supporting the biological plausibility of oxidative stress playing a role in schizophrenia and bipolar disorder (Cabungcal et al., 2006; Steullet et al., 2010).

As such, it may be clinically useful to monitor oxidative stress in both disorders. Most measures of oxidative stress are of a peripheral nature and relating such indices to what is occurring in the brain is challenging. Recently, however, brain lipid metabolism assessed using *in vivo* ^{31}P magnetic resonance spectroscopy was found to be correlated with an index of systemic oxidative stress (Puri et al., 2008a). The marker used was ethane, a product produced by the reaction of omega-3 PUFA (such as eicosanpentaenoic, docosahexaenoic, and alpha-linolenic acid) with free radicals (Halliwell and Gutteridge, 1999). Ethane levels have been shown to be elevated in schizophrenia in agreement with the hypothesis of increased oxidative stress in the disorder (Puri et al., 2008b). Given that ethane is highly volatile and rapidly passes from cells to the blood stream and hence cross the alveolar membrane in the lung, it can be detected in the breath (Dillard et al., 1977; Wade and van Rij, 1985; Ross et al., 2003). Breath analysis is an emerging methodology which, being non-invasive and rapid, is ideally suited to clinical monitoring (Amann et al., 2007). Measuring the breath concentration of this compound may represent a useful means to examine oxidative stress in schizophrenia and bipolar disorder. Although preliminary data is available for schizophrenia, no studies of breath ethane in bipolar disorder have been undertaken. Furthermore, given that ethane production in response to lipid peroxidation is related to cellular omega-3 levels and these levels can also be raised by increasing body levels of omega-3 PUFA (Burns and Wagner, 1991 but see Allard et al., 1997), it is unclear as to whether ethane levels are elevated in schizophrenia or bipolar disorder due to lipid changes or to oxidative stress. In addition, as described above, PUFA levels are known to be altered, albeit decreased, in both schizophrenia and bipolar disorder, changes which could also influence ethane production. As such, in this study breath ethane levels and, as a comparator, butane, were measured in patients with schizophrenia and bipolar disorder along with omega-3 PUFA abundance.

2. Methods

2.1. Participants

All subjects (including healthy controls, patients with schizophrenia and patients with bipolar disorder) were recruited by invitation and gave informed written consent to participate according to a protocol approved by NHS Highland's ethics board. Subjects were free from significant physical illness at the time of testing, in particular no subject suffered from pulmonary disease. Patients with schizophrenia and bipolar disorder met DSM-IV criteria (American Psychiatric Association, 1994) for each disorder. Healthy controls had no current mental illness or a history of mental illness. All patients with schizophrenia or bipolar disorder were in receipt of a range of psychotropic medications. Symptom severity was determined in (a) patients with schizophrenia using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), and the Clinical Global Impression scale (CGI) (Guy, 1976) and (b) in patients with bipolar disorder using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1980), the Young Mania Rating Scale (YMRS) (Young et al., 1978) as well as the CGI. Based on the YMRS and HDRS, the state of the patients with bipolar disorder included manic (4), depressed (2), mixed (3), and euthymic (6). All subjects were asked whether they smoked tobacco products and, if so, how many they smoked per day.

2.2. Breath analysis

Measurements of breath alkane levels were conducted as previously described (Ross et al., 2003; Puri et al., 2008a, 2008b). Breath samples were obtained from subjects using a syringe system (Markes International Ltd., UK) of volume 130 ml equipped with a disposable mouthpiece. The subjects were instructed to exhale in one long breath into the syringe, until they could no longer breath out, to collect the alveolar (end-expired) air from the lungs. For subjects who smoked breath samples were obtained at least one hour following the last smoking activity. The measured volume of expelled air was then injected into a Perkin-Elmer (UK) automatic thermal desorbtion (ATD) tube packed with Carbotrap 300. Gas samples were analysed using a Perkin-Elmer Auto System XL equipped with a Turbo Mass mass spectrometer and ATD 400 automatic thermal desorbtion. ATD tubes were desorbed onto the cold trap at 320 °C, the cold trap being held at 5 °C. The trap was then rapidly heated to 350 °C and the liberated volatiles injected onto a 30 m × 0.32 mm PLOT GQ column with helium flow rate at 2 ml/min. The oven was set at 45 °C for 10 min and ramped at 14 °C per minute to 200 °C where it was held for 2 min. Ethane eluted at 2.6 min and was identified and quantified by mass spectrometry at *m/z* 30 with comparison to a standard curve (0–60 pMol) constructed using an authentic C1-C6 alkane standard mix (Supelco, UK). Similarly, butane eluted at 9.6 min and was quantified using *m/z* 43. Representative chromatograms are shown in Fig. 1.

2.3. Fatty acid analysis

Erythrocyte fatty acid levels were determined using GCMS analysis of methylester fatty acid derivatives as previously described in detail (MacLean et al., 2003). Venous blood was collected from all subjects into a tube pre-treated with EDTA. The samples were kept on ice for no more than 60 min then spun in a centrifuge at 1500g_{av} for 15 min at 4 °C. The plasma layer and the buffy coat were separated off and the red cells washed with an equal volume of 0.9% saline. Samples were stored at −80 °C prior to analysis in keeping with the method described by Manku et al. (1983). On thawing, the red cells were suspended in 1.8 ml of 17 mM NaCl/1 mM H_2SO_4, and then shaken with 3 ml methanol. Six ml

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