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Sex differences in lipid peroxidation and fatty acid levels in recent onset schizophrenia

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ABSTRACT

Sex differences in the symptomatology and course of illness have been reported among schizophrenic patients. Hence, the principal objective of the present study was to investigate sex differences in the concentrations of the lipid peroxidation metabolites MDA and 4-HNE, and in the membrane phospholipid levels of ARA, EPA and DHA in patients with schizophrenia. A total of 46 paranoid schizophrenics (25 women) with short-term evolution who were in an acute psychotic stage and 40 healthy controls (23 women) participated in the study. Psychopathology was evaluated by BPRS and PANSS. Lipid peroxidation sub-products (MDA, 4-HNE) and fatty acid levels (ARA, EPA, DHA) were determined in erythrocyte membranes. The men in both groups showed higher lipid peroxidation levels and those values were higher in schizophrenic patients than controls, with only EPA fatty acid concentrations found to be lower in the former than the latter. These results suggest that men may suffer greater oxidative neuronal damage than women, and that this could worsen the course of illness and result in greater disease severity.

1. Introduction

Oxidative stress is a state in which a dysequilibrium exists between pro-oxidant processes and the antioxidant defense system that favours the former. It generally occurs as a consequence of an increase in the production of free radicals, or when the antioxidant defense system is inefficient, or a combination of both events (Reddy and Yao, 1996). Oxidative stress leads to lipid and protein oxidation in cell membranes due to reactive oxygen species (ROS) that adversely affect cellular functions such as second messengers in signal transduction (Krejsa and Schieven, 1998), synaptic transmission, and dopamine and GABA transport (Rafalowska et al., 1989). Also, it is considered a mediator of neuronal death (Buttke and Sandstrom, 1994). The increase of lipid peroxidation metabolites such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) induces higher susceptibility to neuronal damage, mitochondrial dysfunction and, consequently, neuronal death (Keller et al., 1999).

Substantial evidence suggests that schizophrenic patients show higher indexes of oxidative stress that may contribute to the deterioration observed over the course of the disease (Bitanihirwe and Woo, 2011; Dietrich-Muszalska et al., 2009; Mahadik and Mukherjee, 1996; Othmen et al., 2008; Pedrini et al., 2012; Raffa et al., 2012; Sarandol et al., 2007; Zhang et al., 2010) and may be associated with cognitive impairment in these patients (Zhang et al., 2012). Disorders in antioxidant defense mechanisms have been described in the plasma of first episode patients (Reddy et al., 2003) in those undergoing neuroleptic treatment (Gama et al., 2006; Kropp et al., 2005; Mahadik and Mukherjee, 1996; Pall et al., 1987), and even in individuals with a schizophreniform disorder (Mahadik et al., 1998). Moreover, increases in lipid peroxidation levels in the plasma and cerebrospinal fluid have been reported in unmedicated patients with recent onset disease (Dadheech et al., 2008; Li et al., 2006; Mahadik et al., 1998). Other studies have reported a reduction of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-px) and catalase (CAT), in the plasma of untreated schizophrenic patients and others treated with both typical and atypical antipsychotics (Dietrich-Muszalska et al., 2005; Padurariu et al., 2010; Raffa et al., 2009; Virit et al., 2009; Wu et al., 2012; Zhang et al., 2006). Additional evidence is provided by the association between negative symptom severity and oxidative stress (Mahadik et al., 1998; Pazvantoglu et al.,

Abbreviations: MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; ARA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Symptom Scale; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SCH, schizophrenic patients; CON, healthy controls; SOD, superoxide dismutase; GSH-px, glutathione peroxidase.

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2009; Sarandol et al., 2007). Positive symptoms have also been related to low antioxidative capacity in first-episode and chronic schizophrenics (Pavlović et al., 2002; Ustundag et al., 2006; Virit et al., 2009; Wu et al., 2012). Regarding schizophrenia subtypes, Ustundag et al. (2006) reported higher total plasma antioxidant response levels in the paranoid subtype compared to other schizophrenia subtypes and Pazvantoglu et al. (2009) found higher oxidative stress index in residual subtype compared to patients with the paranoid subtype. In addition, Medina-Hernández et al. (2007) found higher concentrations of lipoperoxide byproducts (MDA and 4-HNE) and neuron specific enolase in neuroleptic refractory patients compared to both good responders to typical neuroleptics and healthy controls. Oxidative stress appears to become greater as schizophrenia becomes more chronic (Wu et al., 2012).

Other authors have also found failures in the antioxidant mechanisms of the uric acid in schizophrenics treated with haloperidol, and in unmedicated patients, as well as an increase of SOD in erythrocytes, findings that suggest a failure in the antioxidant mechanisms that produce oxidative cellular damage (Gama et al., 2006; Pavlović et al., 2002; Yao et al., 1998).

The oxidative cellular damage caused by ROS affects the polyunsaturated fatty acids (PUFAs) in cell membrane phospholipids, proteins and DNA (Mahadik and Mukherjee, 1996). PUFAs such as arachidonic acid (ARA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may play a role in nervous system activity, improve cognitive development and reference memory-related learning, increase neuroplasticity of nerve membranes, contribute to synaptogenesis and are involved in synaptic transmission (Mazza et al., 2007). PUFAs participate in several functions related to ionic Na/K channels, cAMP, ATPase, membrane receptors and transporters. Therefore, alterations in the PUFAs would affect neurotransmission and dopamine, serotonin and glutamate modulation (Horrobin, 1998; Skosnik and Yao, 2003). EPA, DHA and ARA have potent neuroprotective and cytoprotective actions and prevent apoptosis of neurons and may have an important role in brain growth and development (Das, 2013).

Some studies have reported PUFAs reduction in the red cell plasma membranes of drug naïve and chronically-medicated schizophrenic patients (Arvindakshan et al., 2003; du Bois et al., 2005; Horrobin et al., 1991; Kale et al., 2010; Khan et al., 2002; Peet et al., 1995; van der Kemp et al., 2012). Other research has demonstrated an increase of phospholipase A_2 activity and an accelerated breakdown of membrane phospholipids in schizophrenia (Fenton et al., 2000; Gattaz et al., 1995; Ross et al., 1999). On the other hand, there may be a failure in essential fatty acid incorporation in this disease due to a deficiency of the lipoprotein lipase enzyme (Horrobin, 1998).

Studies conducted with spectroscopic magnetic resonance (^{31}P SMR) in never-medicated patients have demonstrated a reduction in phosphomonoesters and an increment of phosphodiesters in the frontal lobe (Keshavan et al., 2000; Pettegrew et al., 1991), alterations that may reflect an accelerated phospholipid metabolism in these patients. However, Yacubian et al. (2002), in contrast, reported a reduction of phosphodiesters in the left frontal lobe in drug-naïve patients and an increase of ATP that could suggest higher energy demand in the frontal lobes related to more pronounced negative symptoms and cognitive deficits. Yao et al. (2002), meanwhile, found an association between the decrease in the phospholipid polyunsaturated fatty acid content of red blood cell membranes, and the decrease in phosphomonoesters and the product of the breakdown of phosphodiesters of membrane phospholipids in the prefrontal region of first-episode, neuroleptic-naïve schizophrenic subjects.

As mentioned above two important indexes of oxidative stress are PUFAs depletion and the increase in lipid peroxidation products in cell membranes, together with the antioxidative enzymes that have been found to be altered in schizophrenic patients. Therefore in the present study we decided to use the combination of the two former indexes to evaluate oxidative stress. Among the PUFAS most commonly used to evaluate oxidative stress in schizophrenia are ARA, EPA and DHA (van der Kemp et al., 2012), while two of the metabolites that have proven to be more specific and sensitive for measuring lipid peroxidation measurement are MDA and 4-HNE (Ciobica et al., 2011).

On the other hand, several studies have reported sex differences in schizophrenia related to the risk of developing the disease, prodromal symptoms, clinical symptoms, onset and course of illness and treatment response (Choi et al., 2009; Meesters et al., 2012; Sánchez et al., 2012; Soldin and Mattison, 2009) as well as to cognitive and emotional processing (Longenecker et al., 2010; Ramos-Loyo et al., 2012; Seidman et al., 1997; Torniainen et al., 2011). Also, women show better premorbid social adjustment, later onset, and a higher number of spontaneous remissions than men. Moreover, women have better long-term outcomes than men, coupled with lower symptom severity. Schizophrenic men, meanwhile, present more antisocial behaviors and substance abuse, have poorer prognoses and spend more time in psychotic states. (Häfner et al., 1993; McGlashan and Bardenstein, 1990; Thara and Eaton, 1996). Furtheremore, gender dimorphism in brain structures has been reported (John et al., 2008); in general, men manifest more brain morphology abnormalities than women (Lewine et al., 1990). Malaspina et al. (2012) have found sex differences in the association between olfatory processing and cognition that may be related to differences in the connectivity and function of brain structures involved in olfaction in schizophrenic patients. Finally, some evidence indicate that healthy men exhibit higher levels of markers of oxidative stress than women (Sartori-Valinotti et al., 2007).

With regard to fatty acids, experiments with rats show that females have a greater delay and less severity in the destruction of ARA and DHA than males (Huang and Horrobin, 1987). Kale et al. (2010) found lower DHA levels in males compared with females in first-episode patients. A postmortem study by McNamara et al. (2007) demonstrated higher deficits of DHA in the orbitofrontal cortex of schizophrenic males compared to females. In addition, in healthy women fatty acids are synthesized and incorporated more quickly, and are more resistant to depletion (Horrobin, 1998).

In view of the extensive evidence of sex differences in psychopathology, onset and course of illness, cerebral structure abnormalities, and response to medication between men and women, plus the fact that males may suffer greater oxidative damage and lower phospholipids in their cell membranes, the aim of the current study was to assess sex differences in lipid peroxidation metabolite concentrations (MDA, 4-HNE), and cell membrane fatty acids (ARA, EPA, DHA), in recent-onset schizophrenic patients in acute psychotic states.

2. Methods

2.1. Participants

Schizophrenic patients admitted to the Guadalajara Mental Health Center of the Mexican Social Security Institute (IMSS) in an acute psychotic stage participated in the study. Forty-six paranoid schizophrenics (SCH) with short-term evolution (6 months to 4 years) were included in the final sample: 21 men and 25 women. All of the patients were in an acute stage and unmedicated for at least 2 weeks. Also 40 healthy controls (CON): 17 men and 23 women aged 18-to-45, according to patient´s age were evaluated.

Pregnant women and those with menopausal symptomatology were not included. Also patients who had been subjected to electroconvulsive therapy within the previous 6 months, or that presented severe psychiatric comorbidity were excluded. All patients and controls with neurological or chronic-degenerative disorders, addictions, carcinoma, diabetes, infections or elevated cholesterol, triglyceride and glucose levels were also excluded. Finally, to be considered for inclusion in the sample, potential subjects were required to smoke no more than 3 cigarettes/24 h, or have over 3 alcoholic drinks per week.