



Oxidative and nitrosative stress biomarkers in chronic schizophrenia



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ABSTRACT

There is evidence that the acute phase of schizophrenia (SCZ) is accompanied by specific changes in oxidative and nitrosative stress (O & NS) biomarkers. There are, however, no firm data regarding these biomarkers in chronic SCZ. Therefore, this study aimed to delineate O & NS biomarkers in patients with chronic SCZ. 125 outpatients with SCZ and 118 controls were enrolled. The markers included lipid hydroperoxides (LOOH), advanced oxidation protein products (AOPP), nitric oxide metabolites (NOx), total radical-trapping antioxidant parameter (TRAP) and paraoxonase 1 (PON-1) activity. Immune-inflammatory markers known to be altered in SCZ were also measured: leptin, IL-6, soluble TNF receptors (sTNF-Rs) and the chemokines CCL-11 and CCL-3. There were no significant associations between chronic SCZ and the O & NS markers (AOPP, NOx, LOOH) and the anti-oxidants PON-1 and TRAP. Leptin, sTNF-R, CCL-3 and CCL-11 were significantly higher in SCZ. There were significant associations between pro-inflammatory and O & NS biomarkers (leptin/CCL-8 and AOPP; IL-6 and NOx; CCL-3 and LOOH; CCL-3/IL-6/NOx and TRAP). In conclusion, there were significant intercorrelations between inflammatory and O & NS pathways, which play a role in the pathophysiology of chronic SCZ. O & NS markers and the enzyme PON-1 are not useful as biomarkers in chronic stable polymedicated SCZ patients.

1. Introduction

Schizophrenia (SCZ) is a chronic psychiatric disorder with a neuroprogressive course (Davis et al., 2014). Its etiology is multifactorial, with important genetic components. On the top of altered dopaminergic neurotransmission, abnormal functioning of the hypothalamus-pituitary-adrenal axis as well as activated immune-inflammatory pathways (see Stuart and Baune, 2014 for a list of references) and redox cascades have been reported (Leza et al., 2015; Moylan et al., 2014; Tsai et al., 2013). The role that these pathways play in neuroprogression have been specially investigated since they can affect neuronal plasticity, signal transduction and induce apoptosis (Leza et al., 2015; Mahadik et al., 2001; Manji et al., 2012; Sen et al., 2008; Shahani and Sawa, 2012). Several biomarkers have been investigated as potential indicators of trait, neuroprogression and treatment effec-

tiveness. Nevertheless, meta-analyses studies (Miller et al., 2011; Potvin et al., 2008; Zhang et al., 2008) demonstrated an impressive heterogeneity of results in the literature, suggesting that characteristics such as stage of the illness, use of medications and clinical features might be confounding factors.

For oxidative/nitrosative stress (O & NS) markers in early stages of SCZ, Şimşek et al. (2016) reported that untreated adolescents with acute psychosis did not differ from controls in their plasmatic levels of the antioxidants superoxide dismutase (SOD) and glutathione peroxidase (GPx) as well as 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of DNA oxidation.

In first episode psychosis (FEP) patients (i.e., patients that are experiencing psychotic symptoms or a psychotic episode for the first time), peripheral oxidative stress is suggested to be present by data reporting increased SOD activity, enhanced levels of lipid peroxidation

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markers (i.e., malondialdehyde or MDA and thiobarbituric acid reactive substances or TBARS), decreased activity of both GPx and paraoxonase 1 (PON1) as well as lowered total radical-trapping antioxidant capacity (TRAP) (García-Bueno et al., 2014; Noto et al., 2015b; Sarandol et al., 2015). Additionally, García-Bueno et al. (García-Bueno et al., 2014) also reported an increased activity of nuclear factor kappa B (NFκB), a main regulator of O & NS status, in blood mononuclear cells of FEP patients as well as increased nitrite levels. Treatment with risperidone (11 weeks) normalized PON1 activity and decreased lipid hydroperoxides (LOOH), suggesting an anti-oxidant effect (Noto et al., 2015b) of treatment. Sarandol et al. (Sarandol et al., 2015) did not observe alterations in SOD, MDA and GPx after short-term antipsychotic treatment (6 weeks). Kriisa et al. (2016) did not observe significant differences between controls and FEP patients in serum total antioxidant capacity, peroxides and some oxidative stress indexes but they observed significant improvements in oxidant/antioxidant balance after 7 months of antipsychotics treatment.

In SCZ, meta-analysis studies reported nitric oxide and lipid peroxidation to be increased and seric total antioxidant status (TAS) to be increased after antipsychotic treatment (mainly olanzapine and risperidone) approximately 2.5 months after acute psychosis (Flatow et al., 2013). Higher levels of lipid peroxidation and protein carbonyl at early (within first 10 years of a psychotic episode) and late stages of SCZ in the absence of TRAP alterations were observed by Pedrini et al. (2012). Moreover, a meta-analysis published by Coughlin et al. (Coughlin et al., 2013) described that TAS, red blood cells catalase activity (CAT) and plasma nitrite are state markers of SCZ whereas red blood cells SOD appears to be a trait marker because its levels were decreased in FEP, acutely relapsed inpatients and stable outpatients.

Our group has been investigating the profile of various cytokines, chemokines and O & NS markers in different stages of SCZ. FEP patients presented significantly higher IL-6, IL-10 and TNF-α levels as well as TRAP than healthy controls and lower serum activity of PON1 (Noto et al., 2015b). Moreover, an inverse association between PON1 activity and the levels of IL-4, IL-6 and IL-10 was observed (Brinholi et al., 2015). FEP patients treated with risperidone for 11 weeks presented increased activity of PON1 and decreased levels of IL-6, IL-10, TNF-α and lipid hydroperoxides (Noto et al., 2015b). In chronically-treated SCZ patients, we observed increased levels of IL-6, soluble tumor necrosis factor receptors (sTNF-R), leptin and the chemokines CCL-11 (eotaxin) and CCL-3 (MIP-1α), whereas the levels of IL-2, IL-4 and IL-10 were decreased (Noto et al., 2015a). Moreover, using the combination of five biomarkers (sTNF-R1, sTNF-R2, CCL-11, IL-10 and IL-4) we were able to predict the diagnosis of SCZ with a sensitivity of 70.0%, whereas the increased levels of sTNF-R1, sTNF-R2 and CCL-3 were related to treatment resistance (Noto et al., 2015a).

In this study, we focused on some O & NS markers in patients with chronic SCZ versus controls in order to delineate their use as potential biomarkers for chronic SCZ. These markers were chosen because they have been investigated by our group in other neuro-immune diseases as well. O & NS damage to plasmatic lipids (lipid hydroperoxides) and proteins (advanced oxidation protein products) were evaluated as well as the antioxidants TRAP and PON-1 activity. We also examined possible associations between immune-inflammatory markers (leptin, IL-6, sTNF-R1, CXCL-8, CCL-11 and CCL-3) already described in our study population (Noto et al., 2015a) and these O & NS markers.

2. Methods

2.1. Subjects

All patients (125) were recruited at the PROESQ (Schizophrenia Program), an outpatient unit at the Universidade Federal de Sao Paulo, Brazil. The diagnosis of SCZ was established according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) using its Structured Clinical Interview (SCID).

Medical records and familial informants were contacted when necessary. Patients were stable and 41.2% fulfilled remission criteria (Andreasen et al., 2005). The mean age of onset was 22.65 (SD: 8.55), and mean time of illness was 11.75 years (SD: 8.29). Since PROESQ is a specialized center, there is a higher level of treatment resistance (TR) than in regular services. In our sample 56.9% fulfilled criteria of TR and 38.5% were under clozapine treatment. All the others patients were under distinct antipsychotic treatment, including both first and second generation antipsychotics.

The comparison group consisted of 118 healthy volunteers (HC) who neither themselves nor their first-degree family members had a current or previous history of a major psychiatric disorder, including dementia and intellectual disability, according to SCID-I.

Acute and chronic general medical conditions associated with an imbalance in inflammatory responses such as infections, HIV, allergies, pregnancy or the postpartum period, rheumatologic or immunological conditions were exclusion criteria for both cases and controls. In addition, individuals who were under treatment with immunomodulatory drugs were also excluded.

This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Research Ethics Committee of UNIFESP approved the research protocol, and all participants provided written informed consent prior to the enrollment.

2.2. Laboratory measurements

A blood sample of 10 mL was withdrawn from all individuals. Blood was immediately centrifuged, and the serum was aliquoted and stored at -80 °C until thawed for the biomarkers assays.

The O & NS markers measured were advanced oxidation protein products (AOPP), lipid hydroperoxides (LOOH), nitric oxide metabolites (NOx), total radical-trapping antioxidant parameter (TRAP) and the activity of PON-1. AOPP was quantified in a microplate reader (EnSpire, Perkin Elmer, USA) at a wavelength of 340 nm (Hanasand et al., 2012) and is expressed in mM of equivalent chloramine T. LOOH was quantified by chemiluminescence in a Glomax Luminometer (TD 20/20), in the dark, at 30 °C for 60 min (adapted from Flecha et al., 1991 and Panis et al., 2012) and the results are expressed in relative light units (RLU). NOx was assessed in a microplate reader (EnSpire®, Perkin Elmer, USA) at a wavelength of 545 nm by measuring the concentration of nitrite and nitrate (adapted from Navarro-González et al., 1998) and results are expressed as μM. TRAP was evaluated in a microplate reader (Victor X-3, Perkin Elmer, USA) and results are expressed in μM trolox (Repetto et al., 1996). For the determination of seric PON-1 total activity (i.e., arylesterase activity) the rate of hydrolysis of phenyl acetate was determined in a microplate reader (EnSpire, Perkin Elmer, USA) at 270 nm and 25 °C. The activity is expressed in U/mL based on the phenyl acetate molar extinction coefficient of 1.31 mMol/L cm⁻¹ (Richter et al., 2008).

Cytokines and chemokines (IL-6, CXCL-8, CCL-11, CCL-3, sTNF-R1 and leptin), were measured by ELISA (DuoSet, R & D Systems, USA) according to the procedures supplied by the manufacturer and were expressed in pg/mL.

2.3. Statistics

Differences between controls and SCZ subjects were assessed using ANOVAs (continuous variables) or analyses of contingency tables using Pearson chi-square tests (categorical variables). Multivariate general linear model (GLM) analyses were used to examine the effects of explanatory variables (e.g. demographic data and diagnosis) on dependent variables (e.g. the oxidative stress biomarkers). If significant, tests of between-subject effects (univariate GLM analyses) were used to assess the effects of the significant predictor variables on the dependent variables. Automatic stepwise binary logistic regression analysis was used to delineate the significant risk factors of SCZ as dependent

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