Psychiatry Research 249 (2017) 200–205

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Low levels of serum total antioxidant capacity and presence at admission and absence at discharge of a day/night change as a marker of acute paranoid schizophrenia relapse

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ARTICLE INFO

Keywords:
Schizophrenia
Total antioxidant capacity
Oxidant-antioxidant system
Day/night changes
Acute relapse
Biological markers
Methodology

ABSTRACT

Background: An oxidant-antioxidant system dysregulation has been described as a schizophrenia pathophysiological base. The total antioxidant capacity (TAC) is one measure of the antioxidant capacity of a system. Day/night concentration changes is a biological characteristic of hormones such as melatonin or cortisol. There is no information about TAC day/night changes in schizophrenia.
Aims: Studying the existence of a day/night TAC change in schizophrenia.
Method: Forty-three DSM-IV paranoid schizophrenia inpatients participated in the study. Thirty healthy subjects matched by age and gender acted as control group. Blood was sampled at 12:00 and 00:00 h the day after admission and the day before discharge. Serum TAC was measured by the ABTS radical cation technique and expressed in Trolox mmol/L.
Results: Patients had significantly lower TAC levels at admission and discharge (12:00 and 00:00) than controls. At admission patients had a TAC day/night change, with higher day-time than night-time levels (0.66 ± 0.14 vs 0.60 ± 0.15) as well as healthy subjects (0.83 ± 0.07 vs 0.77 ± 0.11). At discharge patients had a similar TAC level at 12:00 and 00:00 (0.64 ± 0.15 vs 0.63 ± 0.14).
Conclusion: Schizophrenic patients present a deficit of the antioxidant system. The initial presence and the later absence of a day/night change deserves future studies.

1. Introduction

Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, disorganized speech and behaviour, and other symptoms that cause social or occupational dysfunction (American Psychiatric Association, 2013). This disease approximately affects 0.5–1% of the worldwide population. Its biological aetiology is multifactorial and is still under investigation (Falkai and Moller, 2012).

Free radicals (FRs) are compounds with unpaired electrons or an open shell configuration that may have positive, negative, or zero electric charge. Depending on the atom placed at its core, the radical can be described as oxygen, carbon, nitrogen or metal centred radicals (International Union of Pure and Applied Chemistry IUPAC, 1997). The unpaired electrons cause radicals to be highly reactive chemical molecules.

FRs play an important role in several biological processes, such as, the intracellular killing of bacteria by phagocytic cells, lipid peroxidation, and the electron transport system in mitochondria among others (Castro and Freeman, 2001). FRs are continuously produced by the body and an excess of FRs can produce oxidative damage. Non-enzymatic and enzymatic antioxidants serve to protect the organism against oxidative stress due to FRs overproduction (Ghiselli et al., 2000).

FRs have been involved in the aetiology of many medical condi-

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http://dx.doi.org/10.1016/j.psychres.2017.01.043
Received 7 March 2016; Received in revised form 7 November 2016; Accepted 18 January 2017
Available online 19 January 2017
0165-1781/

tions, affecting several medical specialties such as psychiatry (Zhang and Yao, 2013), cardiology (Dohi et al., 2013) and dermatology (Motor et al., 2014) among others.

FRs have been involved in the pathophysiology of schizophrenia (Yao and Reddy, 2011). An excess of FR generation and an impairment of the antioxidant defence system have been reported in schizophrenia (Flatow et al., 2013). FRs may partly be responsible for negative symptoms (Nakano et al., 2010), tardive dyskinesia (Chen et al., 2010), neurological soft signs (Raffa et al., 2012) and cognitive impairment (Zhang et al., 2012).

Increased, decreased or unchanged activity of antioxidant enzymes has been reported in patients with schizophrenia compared to healthy subjects (Akyol et al., 2002). Blood concentrations of specific antioxidants can be measured individually, but those measurements are time consuming and expensive compared to the total antioxidant capacity (TAC) that reflects the contribution of antioxidant capacity of water soluble molecules of plasma/serum, such as albumin, caeruloplasmin, transferrin, protein thiols, uric acid, ascorbate and bilirubin and partially alpha-tocopherol (Erel, 2004). Synonymous of TAC are TAA (Total Antioxidant Activity), TAOP (Total Antioxidant Power), TAS (Total Antioxidant Status) and TAR (Total Antioxidant Response) (Erel, 2004). In this article the term TAC will be used in general to refer to the antioxidant capacity.

Decreased (Al-Chalabi et al., 2009; Ustundag et al., 2006) and unchanged (Pazvantoglu et al., 2009) TAC concentrations have been reported in schizophrenic patients compared to healthy controls.

Several biological variables of the oxidant-antioxidant status such as, malondialdehyde and melatonin present circadian and seasonal rhythms (Morera and Abreu, 2007; Morera et al., 2009). However, there is scanty information about TAC circadian rhythms in humans. A circadian rhythm of serum TAC levels, with significantly higher levels at night (01:00 h) compared to daytime levels (13:00 h), has been reported in healthy subjects (Benot et al., 1999). There is no information about day/night differences in the TAC levels of schizophrenia.

The objective of this research is to study if there are day-night changes in serum TAC levels in schizophrenia patients and whether or not TAC levels change between admission and discharge.

2. Methodology

Forty-eight patients meeting DSM-IV diagnostic criteria for schizophrenia psychosis, paranoid type, took part in the study. All patients were independently diagnosed by consensus of two experienced clinical psychiatrists based on the Structured Clinical Interview for the DSM-IV. Patients were admitted in the psychiatric ward of the Canary Islands University Hospital (CIUH), because of an acute psychotic relapse. Patient's exclusion criteria were: 1) drug abuse, 2) presence of acute or chronic physical pathology, 3) pregnancy, 4) intellectual disability or severe cognitive impairment, 5) following a vegetarian diet, and 6) taking vitamin supplements. The two last criteria have been shown to affect the oxidant/antioxidant balance (Schmidt et al., 2013; Sepehrmanesh et al., 2016). Body mass index (BMI) was considered as a global parameter of healthiness.

From the initial sample of 48 patients, five were excluded (two by drug abuse, one by intellectual disability and two by uncooperativeness). Therefore, the final patient sample was comprised of 43 subjects. A control group of 30 healthy subjects matched by age and gender was chosen among the hospital and university staff known by the investigators. The control subjects were selected in any moment between admission and discharge of the patients. Exclusion criteria were the same as the patient criteria plus having antecedents of psychiatric illness.

The patient's clinical status was evaluated with the Clinical Global Impressions (CGI) scale (Guy, 1976). Both, the severity of psychopathology (CGI-S) and the improvement (CGI-I) of the clinical evolution was evaluated by the same psychiatrist at admission and at discharge. In the admission period patients were treated with antipsychotics accordingly to the clinician's criteria. Four patients were treated only with risperidona, three with quetiapine, two with olanzapine, eleven with a combination of risperidone and chlorpromazine, six with a combination of risperidone plus levomepromazine and diazepam, three with zuclopenthixol plus chlorpromazine and lorazepam, and the rest of patients with a combination of more than two antipsychotics plus anxiolytics or hypnotics.

Because treatment with several antipsychotics is not unusual (Sertan et al., 2015) and to make antipsychotic treatments comparable, antipsychotic doses were transformed into chlorpromazine equivalent doses (CED) (Woods, 2003).

Haematological and general biochemical blood tests were carried out in order to exclude physical diseases.

The protocol study was carried out in accordance with the Helsinki declaration and was approved by the Ethic and Investigation Committee of the CIUH. Written informed consent was obtained from all subjects after full explanation of the study.

TAC was measured to evaluate the antioxidant capacity. After 4 h of fasting, blood samples were collected at 12:00 (light period) and 00:00 (dark period) hours the day after admission and the day before discharge. After each blood extraction, blood was placed in vacutainer tubes without anticoagulant. Blood was allowed to clot at room temperature during 15 min and then was centrifuged at 3000 rpm during 10 min. Serum samples were aliquot in Eppendorf tubes and kept frozen at −35 °C until analysis.

Serum TAC was measured by the ABTS radical cation technique (Miller et al., 1993), with commercially available kits (Antioxidant Assay kit, SIGMA, Madrid, Spain). The principle of the antioxidant assay is based on the formation of a ferryl myoglobin radical from methamyoglobin and the hydrogen peroxide, which oxidizes the ABTS (2,2´-azino-bis[3-ethylbenzthiazoline-6-sulfonic acid]) to produce a radical cation, ABTS.+ which is a green coloured soluble chromogen. This can be determined spectrophotometrically at 415 nm in a microplate spectrophotometer reader (Benchmark Plus, Bio-Rad, Hercules, CA, USA). Antioxidant compounds suppress the production of the radical cation in a concentration-dependent manner and the colour intensity decreases in proportion to this suppression. Trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid), a water soluble vitamin E analogue, serves as a standard (Miller et al., 1993). The intra- and inter-assay coefficients of variation (CV) were 6.96% and 9.13%, respectively. The results are expressed as mmol of Trolox/L. All serum samples were analysed the same day and by the same analyst, who was blind with respect to the characteristics of the samples.

Data were analysed with the 21st version of the Statistical Package for Social Sciences (SPSS, Illinois, Chicago, USA). Multiple comparisons were carried out with an analysis of variance (ANOVA) for repeated measures. If the result was significant, posterior multiple comparisons were carried out according to the LSD (Less Significant Difference) test. Pearson statistic was applied to analyse relationships between quantitative variables. Chi-square was applied to analyse qualitative variables associations. All statistical tests were two-tailed and their significance level was set at 0.05. Quantitative data are presented as mean ± SD.

3. Results

Demographic and clinical data of both samples are presented in Table 1. Patients and healthy controls were comparable by age, gender distribution and Body Mass Index (BMI).

Fig. 1 shows the patients clinical evolution according to their CGI-I and CGI-S scores. Patients improved significantly between admission and discharge in both measures of the CGI.

Healthy subjects had significantly higher TAC levels at midday than midnight (12:00 0.83 ± 0.07 vs 0.77 ± 0.11, $p < 0.01$).

The comparisons of TAC levels at midday/midnight and admission/