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Adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients: A 12-months follow-up study

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ABSTRACT

Correlation of plasma antioxidant enzyme activity with the course and outcome in first-episode schizophrenia patients ($n=49$) was analyzed in order to assess the possible utility of peripheral markers of oxidative stress as prognostic factors. These markers were measured shortly after the onset of schizophrenia, and again 1, 6 and 12 months later. A decrease in catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), and glutathione (GSH) levels and total antioxidant status (TAS), as well as an increase in thiobarbituric acid reactive substances (TBARS), were observed 1 month after ($p<0.05$). 6-Months later, there was a reduction in TAS, GSH, SOD and GPx, and a increase in TBARS ($p<0.05$), with a normalization of CAT levels, indicating a persistent alteration of the antioxidant system and the maintenance of oxidative stress. At 12-months, a considerable decrease was observed in TBARS. Additionally, while the level of GPx decreased ($p<0.05$) further, SOD and GSH levels and TAS were normalizing, indicating a partial regeneration of the antioxidant defence system. These results indicate the possible contribution of oxidative stress to the onset and pathophysiology of schizophrenia, suggesting the involvement of an adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients.

1. Introduction

Biological markers could improve the diagnosis and the clinical management of patients with schizophrenia (Domenici et al., 2010; Arai et al., 2010; Ohnuma and Arai, 2011). It has been suggested that oxidative stress could play an important role in the pathophysiology of schizophrenia (Raffa et al., 2009; Micó et al., 2011). Oxidative stress can be considered as the overpowering of the antioxidant defence system by the oxidative system (Fig. 1). This effect is produced by free radicals, such as reactive oxygen and nitrogen species, which can react with lipids, proteins and nucleic acids causing cell death. Cells produce free radicals continuously (Urso and Clarkson, 2003), and reactive oxygen species have been found to be involved in cancer (Ames, 1998), ageing (Harman, 1956) and the impact of extreme physical exercise (Sastre et al., 1992; Urso and Clarkson, 2003). Neuronal membranes can be altered by free radicals, through lipid peroxidation, leading to functional alterations and even cell death. Due to the fact that these membranes contain a high proportion of polyunsaturated fatty acids, they can be severely damaged by oxidative stress. On the other hand, free radicals are neutralized in cells by the antioxidant defence system, which is expressed through various antioxidant enzymes, such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (Urso and Clarkson, 2003).

The enzyme catalase (EC 1.11.1.6) is tetrameric, with four identical subunits, and catalyzes the conversion of hydrogen

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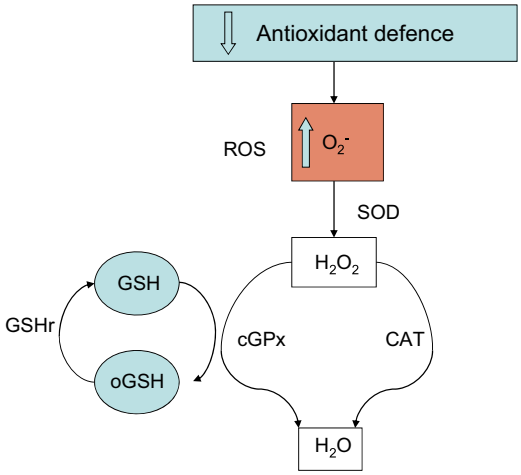

Fig. 1. Schematic representation of the antioxidant defence system. The key for the representation is as follows: ROS (reactive oxygen species), GSH (gluthatione), oGSH (oxidized glutathione), GSHr (gluthatione reductase) and cGPx (constitutive gluthatione peroxidase).

peroxide (H_2O_2) to H_2O and O_2. It cannot be saturated by any H_2O_2 concentration, and consequently it is very useful in the protection of cells against oxidative stress induced by the H_2O_2 produced in intracellular metabolic reactions. Specifically, as CAT captures H_2O_2 before it can escape from the cell, generating O_2, it plays an important role as a protective factor against oxidative stress. SOD (EC 1.15.1.1) is the first line of cell defence against free radicals. It catalyzes the destruction of superoxide radicals, producing hydrogen peroxide, which in turn can be transformed by other antioxidant enzymes, such as CAT or GPx. Three forms of SOD have been described in humans: mitochondrial Mn-SOD, cytosolic Cu/Zn-SOD and extracellular SOD (EC-SOD); EC-SOD, in particular, is considered to be essential for cell survival. GPx (EC 1.11.1.9) is formed by four identical subunits, each of them containing selenium cysteine, which is essential for enzyme activity. It also acts on H_2O_2, and can also reduce various different superoxides using reduced glutathione. Indeed, the glutathione redox cycle is the main protective factor against low levels of oxidative stress in cells. In human erythrocytes glutathione peroxidase is more important than CAT for transforming H_2O_2. The enzyme glutathione reductase (EC 1.8.1.7) reduces oxidized glutathione using reduced nicotinamide adenine dinucleotide phosphate (NADPH). It can also reduce all organic hydroperoxides, taking hydrogen from reduced glutathione.

Both increased production of reactive oxygen species and decreased antioxidant protection, indicated by abnormal activity of critical antioxidant enzymes, have been reported in schizophrenia (Micó et al., 2011), and these alterations suggest a dysregulation of free radical metabolism (Fendri et al., 2006). In line with this, higher plasma levels of malondialdehyde, as well as lower levels of SOD and GPx, have been observed in patients with schizophrenia, suggesting that oxidative stress could underlie the pathophysiology of schizophrenia (Zhang et al., 2006).

This being the case and taking into account that peripheral blood is easy to obtain and provides a large pool of biomarkers in the form of antioxidant enzymes, we measured plasma levels of these enzymes in patients with schizophrenia during their first episode and over the following year. The aim was to assess adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients. Specifically, plasma levels of several antioxidant enzymes: CAT, erithrocyte catalase (CATe), GPx and SOD, of thiobarbituric acid reactive substances (TBARS), and of glutathione (GSH), as well as total antioxidant status (TAS), were measured shortly after the onset of patients' first-episode of schizophrenia and again 1, 6 and 12 months later, in order to investigate potential changes in oxidative stress and the antioxidant defence system.

2. Methodology

Peripheral whole-blood samples were collected from patients upon arrival at the emergency room and again 1, 6 and 12 months later. A total of 98 patients (mean age ± SEM: 33.22 ± 1.03 years), ranged from 17 to 61 years, from Vitoria-Gasteiz (Spain) who experienced a first psychotic episode were recruited. With respect to the inclusion criteria, first-episode schizophrenia was defined as the first time a patient displayed positive psychotic symptoms of delusions or hallucinations of less than 6 months duration. With respect to the exclusion criteria, only drug-naïve patients were included in the study, although treatment with benzodiazepines was allowed. Other exclusion criteria were: mental retardation, neurological disorders, history of head trauma with loss of consciousness, other concomitant illnesses (including active inflammatory illness), tobacco consumption superior to 20 cigarettes per day, taking anti-inflammatory medication, older age (more than 61 years) and pregnancy or breast-feeding. In addition, the practice of strong physical exercise or sports in the previous week was also considered. The flow of participants through each stage of the study is shown in Fig. 2. The final sample size was $n=49$ [33 (67.35%) men, 16 (32.65% women)]. A number of sociodemographic variables were assessed and are presented in Table 1. Patients were diagnosed with schizophrenia using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (American Psychiatric Association (AMA), 1994). They were treated after the first episode with antipsychotic medications (typical and atypical antipsychotics) following the usual protocol. At 6- and 12-months follow-ups, all the patients were still taking medication as shown in Appendix A. Blood samples were collected by venipuncture from the antecubital vein by the healthcare professionals of Santiago Apóstol Hospital of Vitoria-Gasteiz (Basque Health Service/Osakidetza). After informed consent, blood samples were collected in heparin-containing tubes and centrifugated in all cases within 4 h of collection, following standard procedures. Blood cells and plasma samples were immediately frozen and stored at −80 °C until analysis (all plasma samples were measured in one time) in the research laboratory of the Department of Physiology, at the University of the Basque Country, Spain.

Oxidative stress was assessed by measuring activity of the primary enzymatic antioxidant defence system (GPx, CAT and SOD activities) and plasma levels of TAS, GSH and TBARS. GPx was measured using an assay kit from Cayman Chemical (703102). This kit can be used to measure all of the glutathione-dependent peroxidases in plasma, as GPx activity is indirectly measured by a coupled reaction with glutathione reductase. Specifically, oxidized glutathione (GSSG) produced by GPx is recycled to its reduced state by GR and NADPH. The NADP+ obtained is accompanied by a decrease in absorbance at 340 nm. The catalase activity was measured using a Catalase Assay kit from Cayman Chemical (707002). This kit

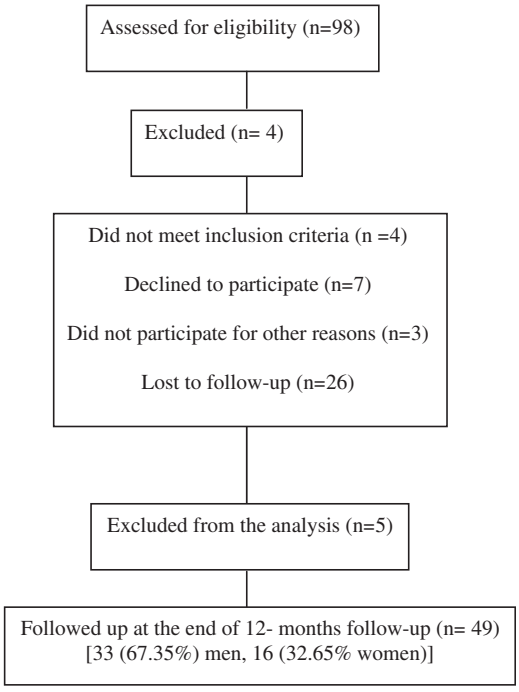

Fig. 2. The flow of participants through each stage of the study ($n=49$).