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Angiotensin converting enzyme activity is positively associated with IL-17a levels in patients with schizophrenia

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ABSTRACT

Previous studies of our group showed increased plasmatic Angiotensin-I Converting Enzyme (ACE) activity in schizophrenia (SCZ) patients compared to healthy controls, which was also associated to poor cognitive functioning. The ACE main product angiotensin II (Ang-II) has pro-inflammatory properties. Activated immune-inflammatory responses in SCZ and their association with disease progression and cognitive impairments are also well-described. Therefore, we examined here the association of plasma ACE activity and inflammatory mediators in 33 SCZ patients and 92 healthy controls. Non-parametric correlations were used to investigate the association of the enzyme activity and the peripheral levels of immune inflammatory markers as interleukins, tumor necrosis factor (TNF-α), and interferon (IFN-γ). Although no significant correlations could be observed for ACE activity and measured cytokines levels in healthy controls, a significant positive correlation for ACE enzymatic activity and IL-17a levels was observed in SCZ patients. Correcting for gender did not change these results. Moreover, a significant association for ACE activity and IFN-γ levels was also observed. To our knowledge, this is the first study to show a significant association between higher ACE activity and the levels of cytokines, namely IL-17a and IFN-γ, in patients with SCZ.

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1. Introduction

Renin–Angiotensin System (RAS) was classically described in the context of water and pressure homeostasis regulation (Basso and Terragno, 2001). Angiotensin-converting enzyme (ACE) is a zinc-dependent carboxydipeptidil peptidase responsible for the conversion of angiotensin I (Ang-I) to the hypertensive peptide angiotensin II (Ang-II), and it was therefore considered as the key element of RAS. More recently, some authors proposed the re-definition of RAS as a stress-response system, as it is extremely relevant to sustain homeostasis with actions on blood pressure, behavior and immune-regulatory system (Bali and Jaggi, 2013).

The relevance RAS in brain has been recently underscored due the association with neurodegenerative diseases, including Parkinson's and Alzheimer's diseases. Several lines of evidence also support a role for RAS in schizophrenia (SCZ), including the modulatory effects of RAS on brain dopamine pathways (Fineberg

Abbreviations: RAS, Renin–Angiotensin System; ACE, angiotensin-I converting enzyme; SCZ, schizophrenia; Ang-I, angiotensin-I; Ang-II, angiotensin-II; ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; FRET, Fluorescence Resonance Energy Transfer; MCP-1, monocyte chemoattractant protein-1; NF-kB, Nuclear Factor Kappa-B; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; GWAS, Genome-Wide Association studies; PANSS, Positive and Negative Syndrome Scale; SCID, Structured Clinical Interview for DSM-IV; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; CBA, cytometric bead array; Treg, antigen-specific regulatory T cells; BMI, body mass index

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and Ellman, 2013; Song et al., 2009), and on neurodevelopment and synapse plasticity (Wright et al., 2013). The several studies addressed to study the ACE role in SCZ produced conflicting results. Most of them suggested higher ACE levels in plasma and cerebrospinal fluid (CSF) of SCZ patients compared to healthy controls (Wahlbeck et al., 1993; Baskan et al., 2010). Recently, we confirmed higher ACE activity levels in SCZ patients compared to healthy controls and that this difference was better understood, but not fully explained, when ACE gene Insertion/Deletion polymorphic genotypes were considered, what can partially explain the previous apparent contradictory findings (Gadelha et al., 2015). However, in which way this higher ACE level correlates to other processes related to SCZ pathophysiology is still not clear.

There is now evidence that the activated immune-inflammatory pathways may play a key role in the pathophysiology of SCZ (Fineberg and Ellman, 2013; Song et al., 2009; Noto et al., 2013). Cytokine levels abnormalities were found in the peripheral blood and CSF of patients with SCZ (Potvin et al., 2008; Miller et al., 2011), and also in their relatives (Nunes et al., 2006). Additionally, Genome-Wide Association studies (GWAS) in SCZ have consistently identified the polymorphisms of major histocompatibility complex genes among the top hits for the comparison with control samples (Ripke et al., 2013). Taken together, it seems that patients with SCZ present a pro-inflammatory monocytic M1 profile, and an imbalance in Th1 and Th2 cells.

Interestingly, besides its primary known hypertensive activity, Ang-II also plays roles as endogenous pro-inflammatory molecule (Das, 2005). In fact, Ang-II infusion elevates the synthesis and concentrations of Tumor Necrosis Factor (TNF-α), interleukin-6 (IL-6), and the chemokine named monocyte chemoattractant protein-1 (MCP-1), which elevates the tissue levels of Nuclear Factor Kappa-B (NF-kB) and the inflammatory cell infiltration (Das, 2005). On the other hand, the ACE inhibitor quinapril inhibits the renal overexpression of TNF-α (Ruiz-Ortega et al., 2002), which may be explained by the suppression of the Ang-II production.

Therefore, our objective in the present work is to evaluate the possible correlation between ACE activity and the immune-inflammatory mediators in patients with SCZ. Our hypothesis is that there is a positive correlation between ACE levels and the pro-inflammatory mediators in individuals with SCZ, which were shown to have both imbalanced immune-inflammatory response and higher ACE activity levels compared to healthy controls (Das, 2005; Song et al., 2009; Noto et al., 2011; Fineberg and Ellman, 2013). Those pro-inflammatory biomarkers with association with ACE activity, and those considered pronounced in our previous results or as reviewed in the literature were chosen for the present work (Miller et al., 2011; Noto et al., 2013; Asevedo et al., 2013; Fineberg and Ellman, 2013).

2. Material and methods

This study was approved by Research Ethics Committee of UNIFESP [CEP No. 1883/10]. Written informed consent was obtained from all participants recruited and, clinical and laboratory investigations were strictly conducted according to the principles expressed in the Declaration of Helsinki.

2.1. Study participants

This sample is part of a larger sample enrolled to multimodal research on Schizophrenia (Gadelha et al., 2013, 2015). Patients were recruited from an outpatient clinic The Schizophrenia Program (PROESQ) of Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP). The inclusion criteria were: (1) aged between 18 and 65 years old; (2) a diagnosis of schizophrenia (SCZ) or schizoaffective disorder according to DSM-IV criteria; and (3) at least one year follow-up. Healthy control volunteers were selected from a governmental unemployment agency and were matched for age, sex and educational level with the patients. The controls were first submitted to interview by phone, which allowed the screening for psychiatric diagnosis, and then they were invited to attend the research center for a full psychiatric interview. The inclusion criteria for the healthy controls were: (1) aged between 18 and 65 years old; (2) no current or lifetime psychiatric diagnosis according to DSM-IV; (3) no family history of psychosis (first, second or third degree). Additional exclusion criteria for both groups were: (1) diagnosis of arterial hypertension; (2) use of any anti-hypertensive medication, even those prescribed for other reasons, e.g. propranolol for tremor; (3) known acute and chronic medical conditions associated with an imbalance in immune system, including infections (e.g. HIV), allergic reactions, pregnancy, the postpartum period, rheumatic disorders, and using medications with immunomodulatory effects such as non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants; (4) reported current abuse of alcohol or use of any drug; (5) lack of consensus on the diagnosis. The full sample for ACE investigation is described in Gadelha et al. (2015) and comprises 86 patients and 100 healthy controls. The collection of material for immune-inflammatory biomarkers was started later and comprises a part of this full sample. Using the above-mentioned inclusion criteria and all samples with available material for the current set of analyses allowed us enroll 33 SCZ patients and 92 healthy controls. No patient or healthy control with available measure on ACE activity or on immune-inflammatory biomarkers was excluded by any of the above-mentioned criteria on current analyses. The Structured Diagnostic Interview, according to DSM-IV diagnosis (SCID), was applied by trained psychiatrists to assess axis I DSM-IV diagnosis. A questionnaire adapted from SCID screening questions was used to investigate family history of mental disease. The clinical assessment for patients also included Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale (CDS) (Bressan et al., 1998), Clinical Global Impression (CGI) (Lima et al., 2007), and Global Assessment of Functioning (GAF). For the diagnosis, we used all available information, including medical records. From the total of included patients, 31 fulfilled criteria for SCZ and 2 for schizoaffective disorders (both diagnosis were analyzed together). Considering mood disorders, 23 did not fulfill criteria for any disorder, 5 patients were currently depressed and other 5 fulfilled for at least one previous depression episode. Considering alcohol/drug abuse or dependence, 1 patient fulfilled criteria for alcohol dependence in the past, and 3 for drug dependence in the past. For any doubt about the diagnosis, even for subtypes, the interview was reviewed by 2 other trained psychiatrists. In all cases a consensual diagnosis was achieved.

2.2. Blood samples

Blood samples were collected from all subjects into heparin vacuum or dry tubes BD Vacutainer® (BD, NJ, USA). The samples were kept at 4 °C, and they were immediately centrifuged at 1500–2000*g* for 10–15 min at room temperature to recover the plasma or serum, which were then stored at −20 °C or −80 °C until use, for enzyme activity and inflammatory markers measurements, respectively. The plasma and serum were carefully removed with a transfer pipette for not disturbing the white blood cells layer or the clot. Although the suggested procedure is to fractionate the blood as soon as possible after collection, some samples were centrifuged up to 24 h after blood collection with no detectable influence in the measured enzymatic activity. The stored samples were defrosted placing the tubes in wet ice soon before the activity measurements as follows.

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