Decreased circulating urokinase plasminogen activator receptor (uPAR) concentration in acute episodes of bipolar disorder; could it be a reflection of axonal injury?

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ABSTRACT

Introduction: In recent years, the role of inflammation in the pathogenesis of Bipolar Disorder (BD) has been studied thoroughly. Urokinase-type plasminogen activator receptor (uPAR) is one of the molecules, whose concentration is of predictive value with regards to an ongoing inflammation and tissue regeneration, and it is hypothesized that it may also be altered in Bipolar Disorder. In this study, it is aimed to compare the levels of serum soluble uPAR during the manic, depressive and euthymic states of cases diagnosed with bipolar disorder, with healthy individuals.

Materials and methods: Forty-four BD patients at manic state (BD-m), 35 BD patients at depressive state (BD-d), 42 euthymic patients (BD-e) and 41 healthy controls (HC) who were similar with the diseased subjects regarding age and smoking status included in the study. Serum soluble uPAR levels of patients and healthy controls were measured.

Results: The main finding of our study is that serum soluble uPAR levels are lower in patients diagnosed with BD either in depressive (BD-d) or in manic state (BD-m) than in BD patients in euthymic state (BD-e) or in healthy controls (HC). There was no significant difference in serum soluble uPAR concentrations between BD-m and BD-d or between BD-e and HC with regards to serum soluble uPAR concentrations.

Conclusions: Urokinase-type plasminogen (uPA) is a molecule which is an element of uPAR system and the molecules collectively take role in inflammation, tissue regeneration and axonal regeneration within the Central Nervous System (CNS). It has previously suggested in some studies that there may be a decrease in axonal density or axonal dysfunction in CNS in bipolar individuals. Accordingly, one may say that the low concentrations of soluble uPAR measured in our bipolar patients either at depressive or at manic state is due to the diminished regulatory role of soluble uPAR on axonal regeneration in CNS of BD cases.

1. Introduction

Although the biological, genetic or psychosocial factors thoroughly studied as a proposed factor which may play role in the pathogenesis of Bipolar Disorder, none of these efforts have been succeeded to point to a definite scheme of the disease pathogenesis. Numerous studies indicate that immunomodulators are involved in mood disturbances and may be responsible for the symptomatology (Singh et al., 2007). Among the previous studies in which the role of inflammation in BD, most of them focused primarily on the cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL) –2, IL-4, IL-6, IL-10, IL-1β or interferon-γ (IFN-γ) (Kim et al., 2007; Ortiz-Dominguez et al., 2007; Valvassori et al., 2015). Previous knowledge cumulatively concludes that cytokine changes deteriorate homeostatic mechanisms, immunological system, neurotransmitter and endocrine systems, eventually cause a neuronal degeneration and impair neurogenesis in BD settings (Kim et al., 2007).

Imaging studies underlined a decrease in white matter in patients with BD. (McIntosh et al., 2005; Stanfield et al., 2009). In a recent study, authors reported that the BD-diagnosed adolescents represent an altered mode of white matter development and have an impaired

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enlargement and evolvement of white matter when compared with the healthy group (Najt et al., 2016). However, in a recent etiological study, it is reported that the axon-related proteins were significantly lower in patients with BD than in the healthy controls. The authors concluded that these findings are suggestive of deficient axon-related proteins in the prefrontal white matter in BD; moreover it is also noted that there may be axonal dysfunction or decreased axonal density in CNS of BD patients (Shao et al., 2016).

The urokinase-type plasminogen activator system is a protease system; and is composed of serine protease urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), and various inhibitors (Bilgili and Cinel, 2013). Soluble urokinase-type plasminogen activator receptor (suPAR) is a membrane protein coupling the glycosyl-phosphatidylinositol (GPI) receptor, which is the soluble form of the urokinase-type plasminogen activator receptor and can be detected in plasma, urine, and cerebrospinal fluid (CSF). These modulators take role in the activation of the immune system (Eugen-Olsen et al., 2002; Persson et al., 2012; Thuno et al., 2009). It was previously reported that the soluble uPAR concentrations measured in serum as well as the Cerebrospinal Fluid (CSF) were correlated with the formation of some neurological disorders. (Garcia-Monco et al., 2002). Elevated levels of soluble uPAR have been reported in many disease settings such as viral infections resulting from immunodeficiency, malaria, pneumococcal and streptococcal pneumonia, sepsis, bacterial and viral CNS infections and active tuberculosis. As a result, one may suggest that soluble uPAR may be a good marker of inflammation (Thuno et al., 2009). Serum soluble uPAR concentrations are stable during the day with limited circadian changes, thus providing an advantage in clinical use (Donadello et al., 2012).

In addition, the role of uPAR in infectious diseases and in inflammatory processes as well as in tissue regeneration is also mentioned (Blasi and Carmeliet, 2002). It is known that uPAR formation plays a regulatory role in inflammation and tissue regeneration in numerous cancers with poor prognosis (Smith and Marshall, 2010). There is also evidence that uPAR plays a crucial role in regeneration of the central nervous system in the way it promotes the rearrangement of the actin cell skeleton following a damage to the dendrites during an ischemic stroke (Wu et al., 2014). In another study, it was emphasized that uPAR plays a critical role not only in the cortical development but also in biochemical pathways (Powell et al., 2003). In a large-scale molecular study, an increase up to seven folds in uPAR during epileptogenesis was reported, and it was concluded that uPAR may play an important role in neuronal tissue rearrangement during epileptogenic processes (Lahtinen et al., 2006). However, in a recent study, in vitro and in vivo data demonstrate that the uPA/uPAR system promotes axonal regeneration in CNS (Merino et al., 2017).

Previous reports of uPA in neuropsychiatric diseases pointed out a polymorphism in urokinase-type plasminogen gene and this polymorphism is suggested to have a role in the pathogenesis of Alzheimer’s, a neurodegenerative disease (Ji et al., 2012). Another study reported that, soluble urokinase-type plasminogen activator receptor levels were higher in schizophrenia patients than in healthy controls (Nielsen et al., 2014). In contrast, another study reported similar soluble uPAR levels in schizophrenia patients and in healthy controls (Genc et al., 2016).

Taken into consideration that uPA and uPAR system is of notable importance in inflammation, tissue regeneration and neural regeneration in CNS; we aimed to compare the serum soluble uPAR measures of BD patients and healthy controls, considering the literature on BD and inflammation relation and the studies showing the damage in axonal proteins in bipolar disorder.

2. Methods

2.1. Participants

Between August 2015 and August 2016, at Bakirköy Mental Health Research and Training Hospital male patients with Bipolar disorder-1 according to DSM-5 diagnostic criteria, in manic, depressive or euthymic states, either from registries of outpatient or inpatient care units, were selected. Male participants aged 18–65 years were included for both study groups. Exclusion criteria were defined as follows: i) mental retardation, dementia or presence of a psychiatric disorder due to a systemic medical condition, ii) alcohol and/or substance abuse, iii) presence of an ongoing infection or allergy of any kind, iv) medical conditions affecting the neurological state or Central Nervous System. As for the healthy controls, volunteers who applied to our outpatient clinic, and were similar with the bipolar group regarding age and smoking status and who does not have a psychiatric diagnosis or a first degree relative with a psychiatric disorder. All participants were informed about the study and asked to fill the informed consent form. The sociodemographics were obtained by the physician. Patients were assessed via Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS). For the euthymic state, it was defined as the euthymic psychiatric condition sustained at least for 8 weeks, and YMRS ≤ 8, HDRS ≤ 7. Blood samples were drawn in the morning at around 8 a.m. from a forearm vein at the end of an overnight fasting period for at least 8 h. Serum uPAR levels, biochemistry and hemogram measures were studied from the blood samples. Statistical analyzes were performed accordingly. The method is primarily based on the caloriometric measurement of quantitative uPAR in human serum concentrations via spectrophotometer in vitro settings. Bakirköy Dr. Sadi Konuk Education and Research Hospital Ethics Committee has approved the study in ethical and scientific terms.

2.2. Statistics

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22 for Windows. Descriptive statistics were presented as mean ± standard deviation, median (min-max). Chi-square test was used to compare smoking status. The Kolmogorov-Smirnov test was used to assess whether the continuous data fit the normal distribution. One-way analysis of variance (ANOVA) and post-hoc Tukey test were performed to compare continuous variables between groups for parametric values. Analysis of Covariance (ANCOVA) was used to statistically adjust for medication when making group comparisons. Kruskal Wallis test was used for comparisons of non-parametric data. Spearman correlation tests were used to evaluate the correlations between variables. Significance level was accepted as p < 0.05.

3. Results

A total of 121 patients who were episode diagnosed as Bipolar Disorder-1 according to DSM-5 diagnostic criteria, 44 in manic, 35 in depressive and 42 in euthymic states were included in this study. Forty-one healthy volunteers who were similar for the age and smoking status with the BD group were included as control group. Only the male subjects were included in the study. The mean age of the groups were similar (38.22 ± 11.37 years for BD-m, 41.54 ± 10.29 years for BD-d, 40.52 ± 10.90 years for BD-e and 39.02 ± 10.69 years for HC, p = .530). There was no statistically significant difference between the groups in terms of smoking (χ² = 4.561, p = .207). Characteristics of groups are represented in Table 1.

In our study, serum concentrations of soluble urokinase-type plasminogen activator receptor were measured for BD-m, BD-d and BD-e, as well as for the HC. Soluble uPAR levels were lower in BD-m (676.8 ± 79.8 pg/ml) and BD-d (675.6 ± 66.5 pg/ml) than in patients in BD-e (757.6 ± 83.4 pg/ml) and HC (752.9 ± 76.4 pg/ml) (p < 0.001) (Table 1).

The levels of soluble uPAR in acute episodes were statistically significantly lower than those in the euthymic episod and healthy control group. Binary comparisons are shown in Table 2.
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