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Research report

The nesfatin 1 level in male patients with manic episode and alterations of nesfatin 1 level after antipsychotic and electroconvulsive treatment

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ABSTRACT

Background: Nesfatin 1 is a newly identified peptide structured satiety hormone that is claimed to be responsible for the provision of appetite and metabolic regulation in hypothalamus. The change in appetite and energy is a well-known clinical feature of affective disorders and within treatment. We aimed to investigate serum nesfatin 1 level in patients with bipolar disorder who were in manic episode and the influences of treatment modalities on nesfatin 1 level.

Methods: Sixty eight patients were elected and were divided into two groups as: antipsychotic treatment (haloperidol 10–30 mg/daily+quetiapine 100–900 mg/daily) arm and ECT+antipsychotic treatment arm. And 30 healthy controls were included in the study.

Results: There was no significant difference according to mean age between patients and controls. Initial nesfatin 1 levels in patients and in both subgroups of patients were statistically lower than in healthy control group. The initial level of nesfatin 1 between ECT+antipsychotic and pure antipsychotic patient groups was not statistically significant. We found a trend of increment in nesfatin 1 level after treatment in both patient groups.

Conclusions: This study is the first that revealed significantly lower nesfatin 1 level in manic episode than healthy controls. ECT+antipsychotic and antipsychotic treatments have no significant effects on nesfatin 1 level after manic episode treatment. These findings should be interpreted cautiously because of small sample size and being drug free only for one week.

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1. Introduction

Nesfatin is a peptide structured satiety hormone that is newly identified as anorexigenic factor which contains 82 amino-acids (Su et al., 2010). In addition to the highly presence of nesfatin at satiety regions of brain in hypothalamic paraventricular, supraoptic, arcuate and lateral nuclei (Oh et al., 2006), it is recently discovered in central amygdala nucleus, caudal raphe nucleus, locus coeruleus and periaqueductal gray matter (Brailoiu et al., 2007) that may be evidence of broad physiologic effects of nesfatin in the body. In rats, the permeation of nesfatin 1 is found to be in a non-saturable process between blood and brain and nesfatin was suggested to be relatively stable in circulating blood (Pan et al., 2007). Nesfatin 1 was claimed to be responsible for the provision of appetite and metabolic regulation in hypothalamus (Brailoiu et al., 2007) and decreased food intake was shown in rats after nesfatin 1 administration intracerebrally (Oh et al., 2006). It is well described that impaired appetite and metabolic deregulations are quite common in affective disorders. Mania is considered to be inflammatory condition accompanied by increased neuroprogression and apoptosis (Berk et al., 2011) and Nesfatin-1 has been demonstrated to possess anti-inflammatory and anti-apoptotic effects in the rat brain with subarachnoid hemorrhage (Tang et al., 2012). Furthermore, nesfatin-1 induces stress-related behavior, like anxiety and fear (Merali et al., 2008) and is related to the severity of panic attack level (Bez et al., 2010) and depressive states (Ari et al., 2011).

In treatment protocols, typical or atypical antipsychotics combination with mood stabilizer and/or electroconvulsive therapy (ECT) may be considered in patients with bipolar affective disorder (Vacheron-Trystram et al., 2004). However, antipsychotics or ECT may have some unwanted effects such as sedation, weight gain, changes in blood glucose level or lipid parameters (Vacheron-Trystram et al., 2004; Ghanizadeh et al. 2012). The change in

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appetite and energy is a well-known clinical feature of affective disorders which warrant to be investigated in relation with nesfatin1 level that has been reported to have influences on energy expenditure (Stengel and Taché, 2010). In the current study, we aimed to investigate, for the first time, serum nesfatin 1 level in patients with bipolar disorder who were in manic episode and the influences of treatment modalities on nesfatin 1 level. Here we hypothesized that: (i) nesfatin 1 level should be lower in patients with manic episode than healthy controls, (ii) nesfatin 1 level should be increased significantly between initial and post treatment phases of manic episode, (iii) in patients with manic epiodes there should be differences in nesfatin 1 level according to treatment modalities (*i.e.*, antipsychotic treatment *vs* antipsychotic treatment+ECT).

2. Methods

2.1. Participants

Two hundred thirty five patients with bipolar affective disorder (BAD) with mania in the current episode according to DSM-IV criterion, who have been hospitalized in Bakırkoy Research and Training, State Hospital from March 2011 to March 2012, were screened for the study. Inclusion criteria were: (i) age between 18–65 years, (ii) being drug free, at least for one week, (iii) for standardization, indication of haloperidol (HAL) and quetiapine (QUET) concomitant use, (iv) or indication of ECT. Exclusion criteria were: (i) alcohol and/or substance dependence or other axis 1 disorder, (ii) having medical disease (diabetes mellitus, thyroid, Cushing and other endocrinological disease), (iii) any extraordinary state needed to change the treatment protocol (*i.e.*, akathisia, acute dystonia, dyskinesia, inadherence to treatment). Sixty eight patients were elected according to the criteria of the study of which five of them drug naïve and rest of them were drug free at least for one week. The patients were divided into two groups as: antipsychotic treatment (standardized as haloperidol 10–30 mg/daily+quetiapine 100–900 mg/daily) arm and ECT arm standardized as haloperidol 10–30 mg/daily+quetiapine 100–900 mg/daily+ECT. The ECT indications for mania were performed according to American Psychiatric Association (APA) as: suicide thoughts with impulsive acts, psychotic features, excessive and exhaustive agitation, rejection of food/water intake, or preference of the patient (American Psychiatric Association, 2001). The patients were assessed according to Young Mania Rating Scale (YMRS) (Young et al., 1978) in Turkish version (Karadag et al., 2002). Additionally, 30 age, gender matched healthy controls participated in the study. Total biochemical evaluation, hemogram and electrocardiogram were carried out for all participants.

2.2. ECT procedure

Electroconvulsive therapy was performed between 8:00 and 11:00 a.m. ECT indicated manic patients ($n=22$) were asked to fast for at least 8 h; none of them was wearing dentures, contact lenses or any ornament and all were wearing hospital clothing. The procedure room was equipped with a defibrillator and drugs necessary for cardiopulmonary resuscitation. Technical procedures were performed according to the standard routines of the laboratory. Electrodes were placed bilaterally on the temporal areas for electrical stimulus conduction. Propofol 1 mg/kg was administered as a short-acting anesthetic; atropine was not used as a preanesthetic because it influences heart rate and could mask possible bradyarrhythmias during the procedure. Curarization was done with succinylcholine (0.5 mg/kg). The Guedel airway was used to optimize oxygen ventilation with a mask and Ambu bag during the convulsive crisis; a protective device was placed between the dental arches.

The ECT device has waves of the fixed, biphasic and short-pulse type. Performed electrical charge was ranged from 250 to 350 millicoulombs (mC), and in current of 550–800 mA, with the frequency of 0.5–2.0 s. Seizures were considered effective when lasting more than 20 s. Blood pressure, ECG tracing and oxygen saturation index were monitored before and during each convulsive seizure because ventilation was not interrupted during convulsion. After the seizures, all patients remained under medical and nursing care until complete recovery.

Blood sample for nesfatin 1 level:

The blood samples were drawn in the initial and posttreatment periods who reached remission according to YMRS (<12 points) as mentioned in the study of Berwaerts et al. (2011). Blood samples for nesfatin-1 were drawn in the morning around 8 a.m. from a forearm vein of the participants at the end of an overnight fasting period for at least 8 h. Tubes with 5 milliliters capacity and containing EDTA were used to collect blood. Then the blood was carefully and immediately (in a few seconds) transferred from these tubes to centrifuge tubes containing aprotinin (0.6 TIU/ml of blood). The first tube was stored on ice immediately. Before the centrifuge, the centrifuge tubes were gently rocked several times to inhibit the activity of proteinases. After the centrifuge process at $1600\times g$ rate for 15 min at 4 °C the plasma was obtained and stored at −80 °C until the time of assay. Plasma nesfatin-1 levels were measured using a commercial ELISA kit (Uscn Life Science, Wuhan, P.R.China). Some previous studies in the literature have used ELISA method for measuring nesfatin-1 peptide level (Bez et al., 2010; Ari et al., 2011). The intra- assay coefficients of variation (CV) value was $<10\%$ for nesfatin 1. The inter-assay CV values were as follows: for glucose ($<1.7\%$), for cholesterol ($<1.7\%$), for LDL-cholesterol ($<1.03\%$), for HDL-cholesterol ($<1.3\%$), and for triglyceride ($<1{,}8\%$).

This study was approved by local ethical committee of Bakırkoy Research and Training, State Hospital and all participants and their legal representatives gave written informed consent before the enrollment in the study.

2.3. Statistics

The data were analyzed using the Statistical Package for Social Sciences version 16.00 (SPSS). Significance level was accepted as $p<0.05$. Except nefatin-1 and triglyceride the other parameters between healthy controls and total patients were compared with Student's *T* test and Mann Whitney U test was used for the statistical analysis of nesfatin-1 and triglyceride. In patients, the initial and post treatment fasting glucose, total cholesterol, low and high density lipoprotein levels and YMRS scores were compared with Paired Sample *T* test, only triglyceride and nesfatin 1 levels were with Wilcoxon Signed Rank test. Mann Whitney-*U* test was used to evaluate differences between two treatment arms. The parameters between initial and post treatment period within treatment groups were compared with Wilcoxon Signed Rank test. After logarithmic transformation of the data for normalization, one way analysis of covariance (ANCOVA) was performed for comparisons between groups after adjustment for age, and BMI. In comparison of categorical variables the chi-square test was used. The relationship between the nesfatin-1 levels and YMRS scores in both groups were analyzed by using by Spearman Rank correlations test.

3. Results

There were 68 patients with manic episode who were divided into two groups as: antipsychotic treatment arm ($n=46$) (standardized as

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