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CLINICAL NEUROCHEMISTRY

Neurohumoral Markers that Predict the Efficiency of Pharmacologic Therapy of Depressive Disorders

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Abstract—We present a comprehensive clinical and biological study of 46 patients with depressive disorder (F32-F33: depressive episode and recurrent depressive disorder) during pharmacotherapy. Neurohumoral factors (cortisol, brain-derived neurotrophic factor, serotonin, DHEA and its sulfated form) were determined in serum by ELISA. The severity of the current depressive episode was evaluated using the 17-point Hamilton Depression Rating Scale (HDRS-17); the pharmacotherapy efficacy was evaluated using the scale of the Clinical Global Impression (CGI Scale). We showed that before prescription of pharmacotherapy peripheral blood neurohumoral markers that characterize the state of stress-realizing and stress-limiting systems of the body may be considered as biological predictors of the effective pharmacotherapy of a current depressive episode and used as additional paraclinical examination methods. At higher concentrations of cortisol and serotonin associated with a decrease in the content of neurosteroid dehydroepiandrosterone, the high efficiency of the pharmacotherapy of depressive episode is predicted.

Keywords: depressive disorder, pharmacotherapy, neurohumoral system

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INTRODUCTION

Affective disorders are a serious health problem in modern society due to the high prevalence of depression in the population and the social importance of depressive disorders [1]. One of the priorities of biological psychiatry is to find biomarkers to predict the response to the antidepressant pharmacotherapy in patients with depressive disorders [2, 3]. In this regard, the use of the systemic approach, which reflects the complex multifactorial nature of mental disorders, may lead to advances in biological psychiatry [4]. Depressive disorders are accompanied by changes in the activity of the neurohumoral systems that constitute the biological basis of the stress response of the body [5]. It is known that hormones of the pituitary–adrenal system, neurosteroids, and neurotransmitters change during the pharmacotherapy of affective disorders [6] and may be considered as biomarkers to predict the response to therapy [7, 8]. According to the literature, currently there are a number of contradictory data concerning the prognostic significance of hormones, neurosteroids, and neurotransmitters. As an example, Eckert et al. [9] highlighted the relationship between neuroplasticity and depressive disorders and showed that BDNF levels may be used for the prediction of response to therapy. However, there are studies that indicate a lack of correlation of the BDNF level with the responsiveness to pharmacotherapy with antidepressants [10]. Morita et al. [11] showed that levels of dehydroepiandrosterone sulfate (DHEAS) in plasma may be used as a putative marker of remission in patients with depressive disorders. The study by Shutov and Bystrova [12] showed that the therapeutic efficacy of antidepressants related to the group of the selective serotonin reuptake inhibitors was associated with aggravation of a deficit of serum serotonin. The authors attributed this to the transition of the neurotransmitter from the blood to the cerebral structures followed by the activation of the serotonergic system in these structures.

In order to identify biological markers that predict the efficacy of pharmacotherapy of a depressive episode, we have examined the levels of neurohormonal factors in the blood serum of patients with depressive disorders.

MATERIALS AND METHODS

The study involved 46 patients with depressive disorders (16 men and 30 women) who were undergoing

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Neurohumoral parameters in the responsive and nonresponsive groups prior the start of the pharmacotherapy

Parameters	Responders $n = 38$	Nonresponders $n = 8$	p
Cortisol, nmol/L	690.38 (591.56–852.31)	602.46 (522.09–644.62)	0.06
Serotonin, ng/mL	135.03 (93.65–159.61)	84.58 (66.61–117.15)	0.018
DHEA, ng/mL	7.03 (4.68–8.55)	8.84 (7.71–9.23)	0.015
DHEAS, μg/mL	1.67 (1.24–3.14)	1.74 (1.1–3.45)	0.723
BDNF, pg/mL values are without multiplying to the dilution coefficient	779 (646.33–950)	916.5 (698.25–970.25)	0.165

p, The significance of the differences between groups of responders and nonresponders, the Mann–Whitney test.

a course of treatment in the Mental Health Research Institute clinics. Diagnostic evaluation and verification of clinical depressive disorder (F32-F33: depressive episode and recurrent depressive disorder) was conducted by psychiatrists based on the diagnostic criteria of ICD-10. The average age of the patients was 56 ± 7.6 years. The study was conducted in compliance with the ethical principles for human research according to the protocol approved by the bioethics committee of the Research Institute of Mental Health. The study was conducted at different stages of therapy: when the patients were admitted to the clinic, prior to medication, and at 2 and 4 weeks of the antidepressant therapy (predominantly selective serotonin reuptake inhibitors). The severity of the current depressive episodes was evaluated by the 17-item Hamilton Depression Rating Scale (HDRS-17), the efficacy of the pharmacotherapy was evaluated on the scale of the Clinical Global Impression (CGI Scale), including the CGI-S subscale that evaluates the severity of the current condition of the patient, and the CGI-I subscale that estimates the dynamics of the improvement of the patient's condition. The criterion for the treatment response was a 50% or greater reduction in the starting total HDRS-17 score during the pharmacotherapy. An additional criterion of the therapeutic response was the achievement of a threshold according to the scale CGI-I of 2 points or less.

Blood for laboratory tests was taken from the cubital vein in the morning from 8:00 to 9:00 on an empty stomach. The concentrations of cortisol, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), serotonin, and brain-derived neurotrophic factor (BDNF) were determined in the serum by the enzyme immunoassay (ELISA) using Alkor Bio reagent kits, Diagnostics Biochem, IBL-Hamburg, and R&D Systems. Experiments were performed according to the instructions supplied with the kit with the control of the standard positive and negative sera included in the test systems. ELISA results were evaluated based on an automated microplate spectrophotometer from Epoch BioTek Instruments (United States) at a wavelength of 450 nm. Statistical analysis was performed using SPSS software version 20.0.

RESULTS AND DISCUSSION

Prior to the beginning of the therapy in patients with depressive disorders, the average Hamilton scale of depression score was 19.3 ± 2.1 points, which corresponds to a moderate depressive episode. On the 28th day of the ongoing antidepressant therapy, there was a reduction of the Hamilton scale for depression score to 12.1 ± 1.3 points ($p < 0.05$, Wilcoxon test). The analysis of the average total CGI-I scores showed the following results: on day 14 of the therapy, the mean total CGI-I score was 2.6 ± 0.5 points, while on day 28 of the therapy it was 1.7 ± 0.5 points ($p < 0.05$, Wilcoxon test). Initial mean total CGI-S score and its value after 28 days of therapy were 3.7 ± 0.5 points and 1.9 ± 0.6 points ($p < 0.05$, Wilcoxon test).

According to the dynamics of improvement during treatment, which was recorded using the HDRS-17 and CGI-I scales, patients were divided into two groups: group 1, responders (38 patients, 82.6%) and group 2, non-responders (8 patients, 17.4%). We identified predictors of the effectiveness of pharmacotherapy by assessing neurohumoral parameters in the studied group before the treatment. The concentration of neurohumoral factors in the serum of patients considering the response to the treatment is shown in the table. In the group of nonresponsive patients, the cortisol concentration was lower than this parameter in the first group at the level of a tendency ($p = 0.06$). The content of serotonin in non-responders was significantly different from the concentration of serotonin in responders ($p = 0.018$). The level of DHEA in the nonresponsive group was significantly higher than the corresponding value of responders ($p = 0.015$). No significant differences in the contents of BDNF and DHEAS in groups of responders and nonresponders were found.

Thus, this study confirmed that cortisol, serotonin, and DHEA, which characterize the state of stress-realizing and stress-limiting systems of the body, play an important role in the pathogenesis of affective disorders and are the most informative biological markers. BDNF and DHEAS are involved in the formation of affective disorder, however, according to the obtained results, they cannot be used as a biomarkers

to predict the efficiency of the pharmacotherapy of depressive disorders. Current data on the prognostic significance of humoral factors are very contradictory. As an example, some authors have suggested that the level of BDNF may be used for prediction of the response to therapy [10], while others showed no correlation of this factor with the responsiveness to pharmacotherapy with antidepressants [11]. Others have associated dysfunction of the hypothalamic–pituitary–adrenal system with the severity and duration of affective disorders [13]. We have previously shown that cortisol is a marker of the hypothalamic–pituitary–adrenal system; its level is associated with a type of the affective disorder and the severity of the current depressive episode [14], and the balance of neurosteroids DHEA and DHEAS is affected by the nosological form of the disorder [15]. The study [12] showed that the therapeutic effect of antidepressants did not normalize the levels of serotonin but induced an even greater deficit of serotonin. In our previous study, we showed that serotonin levels of serum were associated with the type of affective pathology, the severity of the current depressive episode, and the presence of atypical depressive symptoms. An improvement in the clinical condition of patients during drug therapy was associated with the recovery of the initially reduced level of serotonin [6]. Our study demonstrated that high concentrations of cortisol and serotonin and reduced levels of DHEA are biological markers that may predict the efficacy of the pharmacotherapy of depressive episodes. Based on the results of this study, we suggested a method for predicting the effectiveness of treatment of depressive episodes [16]. Neurohumoral blood parameters before pharmacotherapy may be considered as biological predictors of effective pharmacotherapy of depressive episodes and used as an additional paraclinical examination method.

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