DOI 10.18699/SBB-2022-560

Protective properties of DCD and LRP2 proteins in schizophrenia and bipolar disorder

Seregin A.A.*, Dmitrieva E.M., Smirnova L.P., Ivanova S.A., Semke A.V.
Tomsk National Research Medical Center, RAS, Mental Health Research Institute, Tomsk, Russia
** apocalips1991@mail.ru*

Key words: bipolar disorder, schizophrenia, proteome, mass spectrometry, serum, biomarker

Motivation and Aim: Schizophrenia and bipolar disorder (BD) are a heterogeneous group of disorders with unclear etiology and pathogenesis, which makes it difficult to diagnose these severe diseases. Proteomic methods can make it possible to identify protein markers associated with the pathogenetic mechanisms of these disorders, which can serve as a basis for the development of new methods for diagnosing and treating schizophrenia and BD [1].
Methods and Algorithms: We analyzed the blood serum of 63 patients with paranoid schizophrenia (F20.0) aged 34[28;40] years and 23 patients with BD (F31) aged 32[21;52] years. Patients were hospitalized in an acute condition and blood samples were taken before the start of therapy. The control group consisted of 25 mentally and somatically healthy volunteers corresponding to the gender and age of the examined groups. For mass-spectrometric analysis of serum, 10 people from each group of patients with schizophrenia, BD and healthy individuals were selected. Sample preparation, mass spectrometry and data analysis were carried out as described earlier in our article [2]. Statistical analysis was performed using a two-tailed unpaired t-test (FDR = 0.05 and S0 = 2). To measure the level of dermcidin in the serum of the study groups, the ELISA Kit for Dermcidin (DCD) SEC896Hu" (Cloud-Clone Corp., USA) was used. The level of Low-density lipoprotein receptor-related protein 2 (LRP2) was determined using the ELISA Kit for Low Density Lipoprotein Receptor Related Protein 2 (LRP2) Hu (Cloud-Clone Corp., USA). The statistical significance of the result of the ELISA analysis was tested by the nonparametric Mann-Whitney U-test.
Results: As a result, more than 1600 proteins were detected during mass spectrometry. Data analysis using MaxQuant and further evaluation of normalized mean LFQ intensities relative to the studied groups revealed unique proteins that differed significantly for each group: 27 proteins specific for schizophrenia and 18 for BD [2]. Proteins found in patients with schizophrenia are mainly involved in the immune response, cell communication, regulation of protein and nucleic acid metabolism. Unique proteins identified in the serum of BD patients are involved in the regulation of DNA synthesis and cell cycle, differentiation of nerve cells, and transport processes across the cell membrane. Many of these proteins are involved in the pathogenesis of psychiatric disorders and 2 of the most interesting proteins were chosen for further study: DCD and LRP2. But a comparison of their levels between groups of patients with schizophrenia, BD and healthy individuals did not show significant differences. Further, we divided the patients with schizophrenia into 2 subgroups: 33 patients with progressive defect (F20.01) and 30 patients with stable defect (F20.02). In patients with schizophrenia with progressive disease, a decrease in the level of DCD (0.9 [0.56; 1.23] ng/ml Mann-Whitney $p = 0.0038$) and a significant increase in the level of LRP2 (146.70

[102.175; 231.702] pg /ml Mann-Whitney $p = 0.026$), as well as a decrease in DCD in patients with a stable defect (0.435 [0.26; 0.73] ng/ml Mann-Whitney $p = 0.048$) compared with healthy controls (LRP2 99.48 [63.65; 142.29] pg/mL, DCD 1.50 [0.62; 3.22] ng/mL). In addition, a decrease in the level of DCD was found in patients with a stable defect (Mann–Whitney $p = 0.045$) in comparison with the group of patients with BD (1.21 [0.53; 2.06] ng/ml).

Conclusion: The protein dermicidin, in addition to its antimicrobial activity, is a factor in the survival of neurons in the event of their damage [3]; its RNA is expressed in the pons varolii and the paracentral gyrus of the brain [4]. Also, the dermcidin-derived peptide Y-P30 was isolated from the cell lines of the nervous system [5]. It is known that Y-P30 has a neuroprotective effect [6] and promotes the growth of neurites from thalamic and cerebellar progenitor neurons [7]. It is likely that the decrease in DCD levels in patients with schizophrenia compared with controls and in patients with schizophrenia with a stable defect compared with bipolar disorder may be associated with more pronounced neuronal damage during the pathogenesis of schizophrenia. However, the role of DCD in this process is yet to be elucidated. LRP2 is involved in the regulation of the development of neural stem cells in the fetus and progenitor cells during maturation [8]. In adulthood, LRP2 regulates the development and migration of neural stem cells located in two key niches, the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus [9] The function of LRPs in neuronal development is poorly understood, but they have the potential to play a regenerative and projective role in neuronal injury in the pathogenesis of Schizophrenia. An increase in LRP2 levels in patients with progressive defect schizophrenia supports this hypothesis. Other works also confirm the involvement of LRP2 in the pathogenesis of schizophrenia [10]. The proteins we have identified can quite possibly be used as biomarkers upon detailed study, and the study of their neuroprotective mechanisms can serve to elucidate the pathogenesis of mental disorders and, probably, to develop new methods of therapy.

Acknowledgements: This research was funded by Grant of RSF No. 18-15-00053-P.

References

1. Loginova L.V. et al. Mass-spectrometric analysis of serum proteins in patients with schizophrenia. *Bull Sib Branch Russ Academy Med Sci*. 2011;31(6):63-68.
2. Smirnova L. et al. The difference in serum proteomes in schizophrenia and bipolar disorder. *BMC Genomics*. 2019;20(7):535. doi: 10.1186/s12864-019-5848-1.
3. Lee Motoyama J.P. et al. Identification of dermcidin in human gestational tissue and characterization of its proteolytic activity. *Biochem Biophys Res Commun.* 2007;357:828-833.
4. Porter D. et al. A neural survival factor is a candidate oncogene in breast cancer. *Proc Natl Acad Sci USA.* 2003;100:10931-10936.
5. Cunningham T.J. et al. Identification of the human cDNA for new survival/evasion peptide (DSEP): studies *in vitro* and *in vivo* of overexpression by neural cells. *Exp Neurol.* 2002;177:32-39.
6. Macharadze T. et al. Y-P30 confers neuroprotection after optic nerve crush in adult rats. *Neuroreport.* 2011;22:544-547.
7. Landgraf P. et al. The survival-promoting peptide Y-P30 enhances binding of pleiotrophin to syndecan-2 and −3 and supports its neuritogenic activity. *J Biol Chem.* 2008;283:25036-25045.
8. Pollen A. et al. Molecular identity of human outer radial glia during cortical development. *Cell.* 2015;1(163):55-67.
9. O'Rourke M. et al. Adult myelination: wrapping up neuronal plasticity. *Neural Regen Res*. 2014;13(9):1261-1264.
10. Gibbons A.S. et al. Density Lipoprotein Receptor-Related Protein and Apolipoprotein E Expression is Altered in Schizophrenia. *Front Psychiatry.* 2010;1:19. doi: 10.3389/fpsyt.2010.00019.