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Evaluation of interactions of aripiprazole, the atypical antipsychotic drug, with the selected antidepressants in the rat models of schizophrenia

Ocena interakcji arypiprazolu, atypowego leku przeciwpsychotycznego z wybranymi lekami przeciwdepresyjnymi w szczurzych modelach schizofrenii

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2.2. Summary

Schizophrenia is an endogenous psychosis affecting approximately 1% of the population. The disease begins in adolescence and has a varied course. The causes of the disease are not fully understood. There are many hypotheses explaining the genesis of the symptoms. The neurodevelopmental hypothesis, which says about the relationship between disorders in the period of neurogenesis and the occurrence of schizophrenia in the future. It is hypothesized that redox imbalances in the early postnatal period may contribute to the onset of symptoms in adulthood. Currently, in the clinic pharmacological therapy is based on the chronic use of neuroleptics, depending on the type of prevailing symptoms. Schizophrenia syndromes can be divided into positive, negative and cognitive disorders. Typical symptoms are often associated with depression in schizophrenic patients. Therefore, it seems justified to use pharmacological therapy consisting of the combined administration of a low dose of an antipsychotic with low doses of antidepressants.

In the present study, two research models were developed using male Sprague-Dawley rats. At the first a short-term symptomatic model, where symptoms characteristic of schizophrenia were induced by the administration of dizocilpine (MK-801). Next a neurodevelopmental model, where puppies were chronically administered L- Butionin- (S, R) -sulfoximin (BSO) alone or in combination with vanoxerine (GBR 12909). The use of these compounds was aimed at lowering the level of glutathione in the cells and thus disrupting the normal redox balance in the developing brain. This disorder translates into the typical syndromes of schizophrenia in adulthood.

Rats were treated with chronic administration of the antipsychotic drug aripiprazole (ARI) together with the antidepressant S-citalopram (ESC) or mirtazapine (MIR). In order to validate the developed models, behavioral tests were performed to assess the presence of negative symptoms of schizophrenia and cognitive disorders (social interaction test, new object recognition test (NOR), open field test). Then, biochemical tests (qRT-PCR and ELISA) were performed to assess the gene amplification of brain-derived neurotrophic factor (BDNF) and the amount of this protein in the frontal cortex and hippocampus in adulthood.

The results obtained in the articles constituting the doctoral dissertation suggest that both acute administration of MK-801 and the reduction of glutathione levels at the early neurodevelopmental stage contribute to the behavioral deficits characteristic of the symptoms of schizophrenia in tests. In the neurodevelopmental model, a reduction in gene expression and

protein amount for BDNF was also observed in selected brain structures in adulthood. Research results show that the reversal of the above-mentioned deficits occurs after administration of a high dose of ARI or a low dose of ARI together with a low dose of MIR or ESC.

The results presented in the dissertation suggest the correctness of the pharmacological therapy used and confirm the compliance of used research models with the assumptions characteristic of animal models of schizophrenia. Published studies may contribute to the application of a new pharmacological therapy in the clinic and may have an impact on the improvement of the health condition and quality of life of patients with schizophrenia.