Popularnonaukowe streszczenie (język angielski)

Schizophrenia is a severe mental disorder which affects about 400 000 people in Poland. This psychosis is characterized by the impaired perception of oneself and the surrounding world as well as by distorted thinking and emotions. The complicated clinical picture of schizophrenia suggests that an extremely complex and ambiguous mechanism may underlay this disease. Furthermore, despite intensive research the search for the basis of schizophrenia has not been successful, so far, what makes it extremely difficult to develop an efficient therapy. Lack of the proper therapy imposes a serious social and economic burden. Clinically, the symptoms of the disorder can be divided into three main categories: positive symptoms (delusions, hallucinations, thought disorder and incoherence), negative symptoms (lack of motivation and deficits in social function, flat affect) and cognitive deficits (impairment of attention, memory and executive functions). Furthermore, approximately 50% of schizophrenic patients, besides the typical symptoms, suffer from comorbid depression, the presence of which not only worsens rehabilitation of patients but also increases the recurrence rate of symptoms. In the therapy of schizophrenia, classical antipsychotic drugs inhibit mainly the positive symptoms but do not affect the negative symptoms or the impaired cognitive processes. In contrast to conventional antipsychotics, atypical antipsychotic drugs, partly alleviate the negative symptoms and slightly improve the impaired cognitive functions. Recent studies suggest that in the treatment of schizophrenia an improvement of patients' mood should also be taken into account, and therefore the administration of antidepressant drugs is strongly recommended. Furthermore, few clinical and preclinical studies demonstrated that the addition of antidepressant drugs with different pharmacological profiles (mirtazapine and/or scitalopram) to the treatment with the atypical antipsychotics, such as risperidone, enhanced the efficacy of the latter drug in alleviating negative symptoms and in the improvement of the cognitive performance, to a much greater extent than when risperidone was given alone. The above data clearly suggest that the administration of some antidepressants in combination with atypical antipsychotic drugs may be of great importance for clinical practice. Hence, continuation of studies on the interactions of the selected antidepressants with other, than risperidone, atypical antipsychotics appear to be reasonable from both practical and theoretical point of view.

The specific objective of the planned research is to check in the animal models of schizophrenia, whether administration of a low dose of aripiprazole, an atypical antipsychotic drug with the unique receptor profile in combination with antidepressants with different pharmacological properties (escitalopram and/or mirtazapine) will produce a synergistic effect in reversing the behavioral and memory deficits assessed in behavioral tests and in biochemical studies. The research will be performed in two rat models, in which the schizophrenia-like changes in behavior and memory will be induced by the model substances commonly used for this purpose. In the first model, termed in the project the short-term symptomatic model, a single injection of the NMDA receptor antagonist MK-801 will be given to adult Sprague-Dawley rats to evoke these changes. As the prevailing hypothesis for the etiology of schizophrenia assumes that both structural and functional abnormalities could be a consequence of multiple interactions between genetic and environmental factors during development that lead to the appearance of characteristic symptoms in the adulthood, the second used model, will be constructed as the new neurodevelopmental model of this disease. Recent studies suggest that the impaired endogenous synthesis of glutathione (GSH), the most prevalent antioxidant in the mammalian body, and the disturbed homeostasis of dopamine (DA) in the brain, the main neurotransmitter playing a significant role in the manifestation of schizophrenic symptoms, can be considered as an important risk factor that acting during early postnatal development may lead to the manifestation of characteristic symptoms of this disease in adulthood. Therefore, to establish the new neurodevelopmental model of schizophrenia, selective inhibitors of GSH synthesis and DA reuptake will be administered chronically, alone or in combination, to male Sprague-Dawley pups during the early postnatal life (between $5^{th}$ and $16^{th}$ day). In the latter model interactions of aripiprazole with antidepressants (mirtazapine/escitalopram) and aripiprazole with N-acetylocysteine (NAC), a precursor of cysteine for GSH synthesis, at behavioral and biochemical levels will be studied in adulthood after chronic administration of these drugs. The brain intra- and intercellular communication, depends on some specialized protein systems, such as the brain-derived neurotrophic factor (BDNF), cAMP response element-binding (p-CREB), antiapoptotic protein Bcl-2, pro-apoptotic protein BAD and serine-threonine protein kinase B (PKB/Akt). The levels of these proteins are changed in schizophrenia and they are modulated by antipsychotic and antidepressant drugs, therefore, we plan to determined them in the selected brain structures of rats treated chronically with the studied drugs.

We hope that this set of experiments will bring a new quality to basic research and will help to better understand the mechanism of action of both antipsychotics and antidepressants. If positive results of the interaction of aripiprazole with selected antidepressants or aripiprazole with NAC are obtained, an alternative therapy of negative and cognitive symptoms of schizophrenia, may be proposed, which would be especially propitious because the treatment of schizophrenia is currently a serious clinical problem.