ABSTRACT – Karolina Sławińska "*The influence of cannabinoid receptors CB_1 and CB_2 on the effect of selected antidepressants in depression tests on mice*"

Depression is a serious affective disorder. It is estimated that more than 5% of people in the world suffer from depressive conditions. Moreover, in recent years, a continuous increase in the number of patients with the disease has been reported. A serious clinical problem of depressive disorders stems from their chronic and recurrent character and increased risk of suicide. According to statistics, suicidal behaviour occurs in about 10–15% of patients with severe unipolar depression and over 25% with bipolar depression.

The treatment of depressive disorders is difficult and not effective in all cases. Currently used antidepressants show therapeutic efficacy estimated at 60–70%, while clinical improvement in patients occurs only after several weeks of systematic use. Moreover, these drugs are not well tolerated by patients, especially when used for a long time, due to numerous side effects. Therefore, it seems appropriate to search for new antidepressants with different mechanisms of action and to improve existing antidepressants.

Recent reports indicate the involvement of cannabinoid receptors CB_1 and CB_2 in depressive disorders. Numerous compounds, which are selective agonists and antagonists of these receptors, have been tested in both pre-clinical and clinical trials. The results obtained are interesting and promising, however, there is still a need for research on the exact explanation of the mechanisms underlying the antidepressive action of cannabinoids.

The key aim of the present study was to determine the effect of selective cannabinoid receptor agonists and antagonists CB_1 and CB_2 on selected antidepressants. The goal was achieved by using behavioral tests (forced swim test - FST, tail suspension test - TST) in experimental animals (Albino Swiss mice). The nature of interactions between the studied compounds was evaluated based on their concentration in animal brain homogenates using HPLC.

The first part of the research included the evaluation of the influence of cannabinoid receptor ligands CB_1 and CB_2 on mice behavior in FST and TST. The results showed that both agonists (oleamide - selective CB_1 receptor agonist; JWH133 - selective CB_2 receptor agonist) and antagonists (AM251 - selective antagonist/inverse agonist of the CB_1 receptor; AM630 - selective antagonist/inverse agonist CB_2 receptor) show antidepressive activity in both behavioural tests in mice. It was also found that this activity was not related to the change in spontaneous locomotor activity of the animals tested.

In the second part of the experiments the influence of individual ligands of cannabinoid receptors CB_1 and CB_2 on the action of selected antidepressants (imipramine, reboxetine, escitalopram, bupropion, moclobemide, tianeptine, agomelatine) was determined in the above - mentioned tests. It was found that oleamide (a selective CB_1 receptor agonist), intensified the action of most of the antidepressants tested both in the FST and TST. Only in case of simultaneous administration of oleamide with moclobemide and agomelatine, no significant statistical shortening animal immobility time was observed in both tests. On the other hand, AM251 compound - being a selective CB_1 receptor antagonist/inverse agonist - intensified the effects of all antidepressants tested. In the case of cannabinoid CB_2 receptor ligands, it was found that selective CB_2 receptor agonist, JWH133 compound only in combination with imipramine, escitalopram and reboxetine, significantly reduces the statistical time of mouse immobility in FST and TST. On the other hand, AM630 being a selective CB_2 receptor antagonist/inverse agonist combined with imipramine, escitalopram, reboxetine and bupropion significantly reduces animal immobility time in both behavioural tests. This compound, however, did not exacerbate the antidepressant effect of moclobemide in both FST and TST, and in combination with tianeptine and agomelatine intensified the effect of these drugs only in the forced swim test. The obtained results were verified by the spontaneous locomotor activity test in mice to exclude false positive results.

The last element of the work was to carry out pharmacokinetic studies of selected compounds, which concluded that interactions between cannabinoid receptor ligands and most antidepressants are probably caused by modifications at the cellular level. Only the combined administration of oleamide and imipramine resulted in an increased concentration of imipramine in the brain of the animals studied, but this effect was not accompanied by a significant increase in the concentration of desipramine (the active metabolite of imipramine). The results indicate that the observed interactions between CB receptor ligands and antidepressants were of pharmacodynamic character.

In conclusion, the results presented in this study indicate that cannabinoid receptor ligands CB_1 and CB_2 show antidepressant activity in behavioral tests in mice and intensify the activity of most antidepressants belonging to different chemical groups. The results obtained may be an inspiration for further research to clarify the mechanisms of interaction between these compounds and contribute to increasing the effectiveness of treatment in the future and the safety of patients with depression.