New chapter in a long story –

The role of monoamine oxidases palmitoylation during chronic stress

About 3,800 each day and about a million each year people die due to suicide, which is more than because of wars and natural disasters combined. Depression is still a growing health problem nowadays. Over 350 million people suffer from depression worldwide and in Poland up to 1.5 million people. According to the World Health Organization (WHO), depression is currently the leading cause of disability and inability to work in the world and the most common mental disorder. Epidemiological studies show that around 16% of the general population suffers from depression during their entire life. Depression is not only a chronic disease that threatens the lives and proper functioning of individuals in society, but also entails tremendous costs of treatment, social care and inability to work. It is estimated that the annual costs associated with depression are about 1 trillion USD. However, those data are related to the global situation before the COVID-19 pandemic which is also associated with a significant increase in depression cases and suicides number.

The history of antidepressant drugs is over 60 years old and began when the antidepressant properties of anti-tuberculosis drug iproniazid, a monoamine oxidase inhibitor (MAO), were discovered by a lucky accident. This discovery initiated a new era in the treatment of depression. However, after the first years of great optimism regarding the use of MAO inhibitors in anti-depressive treatment, they also showed a dark side. MAO inhibitors were characterized by numerous interactions with other drugs and serious side effects, which significantly weakened initial enthusiasm. The main role of MAO isoenzymes is to participate in the metabolism of neurotransmitters (including serotonin and dopamine), by which monoamine oxidases affect behavior, and disruption of their action may result in the development of neurodegenerative diseases. Although they are no longer the first choice of psychiatrists, they are still used for severe forms of drug-resistant depression and atypical depression. In addition, MAO B inhibitors have been used in the therapy of neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease. Therefore, it is extremely important to improve therapy based on MAO inhibition and reduce its negative side effects. However, to achieve this goal, we need to better understand the mechanisms of action of these enzymes down to the smallest details.

The results of experiments carried out in our laboratory using the mouse model of depression indicate a significant increase in the S-palmitoylation of MAO A and MAO B proteins under stress conditions. S-palmitoylation is one of the post-translational modifications of proteins that may affect their function. Our further analysis showed that the MAO palmitoylation level is tissue-specific, with the highest levels found in the brain in the synaptic fraction. Research in the current project focuses on the detailed characteristics of MAO A and MAO B palmitoylation in both physiological and pathological conditions (during chronic stress). As part of the project, it is also planned to identify the DHHC enzyme responsible for MAOA and MAO B palmitoylation. In addition, the effect of this modification on the enzymatic activity of MAO A and MAO B proteins will be determined. Knowledge acquired in the proposed research will allow to broaden knowledge about these key enzymes in depressive disorders. Despite intensive research on monoamine oxidases lasting almost 100 years, many of their properties and functions are still mysterious for us. The approach proposed in the project is innovative and will be the next chapter in studies about these extremely important enzymes. In the future, it may contribute to the design of antidepressant drugs whose target will be post-translational modifications of monoamine oxidases and it may result in fewer side effects and more effective effects.