Mental disorders still belong to the most important health problems of the 21st century and among them, the soaring incidence of depression is a serious challenge to contemporary medicine. It is known that metabolic processes in the brain are impaired in the course of depression. We suppose that one of the causes of these dysfunctions may be exposure to excessive levels of glucocorticoids during prenatal development. However, guidelines for procedures to be followed when there is a risk of a premature delivery recommend prenatal steroid therapy in every case of threatened premature birth between 24 -34 weeks of pregnancy. Administration of dexamethasone to pregnant women stimulates fetal respiratory maturation, but at the same time increases the risk of depression in adulthood. The effect of exposure to this steroid in the prenatal period on the induction of permanent metabolic alternations in the brain, and the mechanism responsible for the majority of dysfunctions observed in the offspring remain unclear. Epigenetic modifications are one of the candidates' mechanisms that are considered to explain the impact of environmental stress on the risk of depression. Early adverse experiences leave long-lasting epigenetic marks via changes in DNA methylation and histone modifications in the brain. Prenatal treatment with dexamethasone induces persistent genome reprogramming effects resulting in the improper brain cells function but the available data do not explain the mechanisms and consequences of the observed changes. In our project, we postulate that dexamethasone-induced epigenetic processes lead to changes in brain bioenergetics responsible for depression. Additionally, it is also known that there is a link between physical activity and epigenetic modifications of the genome. Epigenetic mechanisms that are affected by exercise can regulate processes that are impaired in depression. In some cases, a positive effect of physical activity can even be compared with efficient pharmacotherapy.

Therefore, the research hypothesis which we plan to investigate in the present project assumes that exposure of animals to dexamethasone during the prenatal period causes epigenetic changes that: (i) alter the expression of factors important in the regulation of brain metabolism, (ii) increase sensitivity of the brain to traumatic stimuli in adulthood and (iii) can be mitigated by physical activity and pharmacotherapy.

Investigating possible differences in the genes' methylation and amount and action of factors that regulate the brain's energy management will allow us to determine the possible new pathways which underlie of depressive disorder. A comprehensive understanding of the mechanisms of epigenetic regulation induced by dexamethasone and establishing the impact of physical activity and pharmacotherapy on observed changes may contribute to finding new targets for personalized treatment in the future.