

Lithium is an efficacious mood stabilizing medication in patients with bipolar disorder. Approximately 30% of patients fully, and further 45% partially respond to the treatment. As stated in NbN nomenclature lithium mechanism of action is unique and multimodal however, the exact mechanism is not known. It acts as a cation, an enzyme inhibitor and modifier of gene expression.

Studies that analyzed changes in the gene expression profile (transcriptome) upon lithium treatment are limited and most of them analyze lithium administration to healthy animals. It means that actually we do not know what happens in a sick organism upon lithium treatment. **Comprehensive analysis of mood/behavior changes and molecular changes is lacking.** Therefore, we plan to investigate animals with depressive-like and manic-like symptoms and molecular changes upon lithium administration. Studies that compare transcriptomic and behavioral changes in animal model with changes that are presented in humans (bipolar patients treated with lithium) does not exist so far. We will analyze both the results from animal tissues (material from brain regions controlling mood and from blood) and from blood samples of bipolar patients (which is material easily accessible from humans) in the course of lithium treatment.

In this project we hypothesize that mood stabilizing lithium mechanism of action impacts gene expression, and it is detectable in several brain areas involved in mood regulation and in peripheral blood. The effect of drug action is a change that one can observe in mood and behavior (depressive/manic symptoms remission). We will seek for correlation between behavioral and transcriptomic changes upon lithium, so the animal model of depression and mania will be applied. The aim of the project is to identify genes involved in lithium mechanism of action. We perform it as prospective observation and analysis of gene expression in brain regions and blood of animals with depressive-like and manic-like behavior. Moreover, we hypothesize that mood/behavioral changes and molecular changes, found in animal model of lithium therapy, correspond with those, which are detectable in peripheral blood of bipolar patients treated with this medication. Genes identified in animal experiment will then be investigated in clinical study. We will seek for correlation between selected genes expression in blood and changes in mood (remission and recurrence) in bipolar patients treated with lithium.

We plan to perform an analysis using animal model and clinical investigation. We will use male Wistar rats. This strain of rats is not genetically modified, so it is suitable to mimic reaction to stress in human general population. Depressive-like symptoms will be induced by Chronic Mild Stress protocol and manic-like symptoms by amphetamine administration, the methods of proven value in translational neuroscience. Then rats will be treated with lithium for 6 weeks. During lithium treatment behavioral changes will be measured (using behavioral tests validated in animal models of depression and mania), as well as transcriptome changes will be investigated (in brain tissue and blood). Transcriptomic analysis in the course of lithium treatment will be performed with expression microarrays. Most significantly altered genes will be analyzed on protein level. Then, we plan to verify the results from animal experiments in the blood from bipolar patients treated with lithium – the clinical study. We will analyze the correlation between the level of gene expression in blood and the changes in psychiatric symptoms (euthymic state and depressive/manic recurrence). The collected data will be analyzed based on statistical and bioinformatics methods. We are aware that in psychiatric studies behavioral phenotype depends on numerous genetic and non-genetic factors and for that reason we plan to collect accurate data about the clinical status. The statistical analyses will be accurately adjusted to analyze the complex results.

Understanding the mechanism of lithium action is crucial for its proper administration, increase in efficacy and avoiding side effects. **This is essential for effective treatment of bipolar patients.** The precise description of biological background of lithium treatment in relation to behavioral symptoms will help develop more personalized approach in the pharmacotherapy of bipolar disorder. The comprehensive investigation of lithium mechanism of action proposed in this project will allow better **understanding of mood disorders** and to develop novel mood-stabilizers. **The innovative aspect of this project is analysis of correlation between mood changes and transcriptomic changes to identify mechanisms of acute and chronic lithium action.** Innovative is also an investigation of correlations between changes detectable in several brain regions and blood. Investigation of relations between molecular and mood/behavior changes allows to describe biological mechanisms responsible for mood stabilizing.