Depression affects more people than all other mental illnesses combined, however, currently available pharmacotherapy or behavioral therapy is not effective in many patients. The low efficacy of pharmacotherapy is probably due to the fact that the antidepressant drugs mainly affect noradrenergic and serotonergic neurotransmission while as indicated by the current study in this disease not only neurotransmission is affected, but also hormonal systems, immune system and metabolic processes are impaired which together lead to numerous functional changes, including depressed mood and impaired cognitive function. The effectiveness of adjunctive treatment of refractory depression with thyroid hormones has been well proven as well as the frequent comorbidity of hypothyroidism in this disease but in contrast to the developmental period, the effects of these hormones in the adult brain are poorly understood. This is due to the fact that it was long believed that after a period of development, the brain is resistant to thyroid hormones. Current clinical studies have provided evidence for both the occurrence of metabolic disorders in depression and their inhibition by thyroid hormones. Experimental studies have shown that these hormones affect many functions in the central nervous system (CSN), including learning and memory, metabolic and neuroprotective processes. Disturbances of metabolic, mainly mitochondrial paths and learning and memory processes are important both in depression and hypothyroidism, so these changes observed in depression may be in fact due to a decrease in the level or activity of thyroid hormones within the brain. **The research hypothesis that we plan to explore in this project assumes that in drug-resistant depression there is a decline in the activity of thyroid hormones in the brain, which can cause disturbances important in the pathogenesis of this disease.**

To verify the above hypothesis, we plan to conduct a study on the Wistar-Kyoto strain of rats, which show the hormonal and behavioral features resembling the symptoms of depression (one of the animal models of drug-resistant depression). We plan to compare selected metabolic, functional and biochemical parameters, significant to the pathogenesis of depression and associated with the action of thyroid hormones, between the Wistar-Kyoto strain of rats and control Wistar strain. Further, we plan to determine these parameters under basal conditions and compare them with respective values obtained in rats in which thyroid hormone synthesis was inhibited by a thyroid peroxidase inhibitor. The effect of the antidepressant drug (venlafaxine) alone and in combination with clinically used thyroid hormone (levothyroxine) on changes in the studied markers will also be examined. Demonstration of metabolic changes in the applied model of depression and the mechanism of their generation may allow for establishing the primary causes of depression, appearing much earlier than changes observed in neurotransmitter levels. Results of the studies on the effects of thyroid hormone deficiency on metabolic and learning and memory processes may indicate the direction of further study and justify the purposefulness of more frequent use of thyroid hormone in the treatment of depression.