1.RESEARCH PROJECT OBJECTIVES/RESEARCH HYPOTHESIS

Depression is a brain disorder that affects hundreds of millions of people all over the world. Recently, it has been shown that depression is characterized by a dysregulation in the oxidative balance. In fact, oxidative stress is enhanced during depression, while antidepressant treatments are connected with normalization of the enhanced biomarkers of oxidative stress. Oxidative stress rises – among others - the synthesis of ceramide in the cell. Some clinical and preclinical studies demonstrate enhancement of the cellular activity of the acid sphingomyelinase (an enzyme enhancing the ceramide level in the cell) in depression, therefore a new hypothesis about the significance of this lipid in the pathogenesis of depression was formed.

The main goal of this project is to investigate if depression and antidepressant drugs alter both oxidative stress and ceramide levels in the brain tissue of laboratory animals. To this end, few preclinical models of depression and repeated treatment with clinically-approved several antidepressant drugs will be studied to determine if the level of oxidative stress markers, the enzymes involved in ceramide synthesis and metabolism pathways and ceramide tissue levels are changed.

2.RESEARCH METHODOLOGY

Two approved animal models of depression (genetic and developed depression), chronic treatments with four clinically-approved antidepressant drugs and several analytical procedures (liquid chromatography-mass spectrometry, radioligand assay, Western blot, spectrophotometry) will be convergent to address:
(i) if the activities of superoxide dismutase and catalase as well as the malondialdehyde concentrations in several brain areas are changed in animals models of depression and in rats treated with antidepressant drugs;
(ii) if the expression of several enzymes involved in ceramide synthesis and metabolism in several brain areas are changed in animals models of depression and in rats treated with antidepressant drugs;
(iii) if the activity of acid sphingomyelinase, alkaline sphingomyelinase and neutral sphingomyelinase in several brain areas are changed in animals models of depression and in rats treated with antidepressant drugs;
(iv) if the levels of ceramide and sphingomyelin in several brain areas are changed in animals models of depression and in rats treated with antidepressant drugs.

3. EXPECTED IMPACT OF THE RESEARCH PROJECT ON THE DEVELOPMENT OF SCIENCE, CIVILIZATION AND SOCIETY

The results of this project will answer if oxidative-stress and ceramide are engaged in the mechanisms related to depression and to action of clinically-approved antidepressant drugs. We hope, that the obtained findings will show new directions in studies on depression as a more comprehensive understanding of the significance of oxidative stress and ceramide pathways to this brain disorder. The outcome from this project may also allow to find new ceramide-derived therapeutic strategies on this devastating brain disorder, lead depression research into new directions and develop much needed targeted therapies for depression.