Depression is included in the category of diseases of civilization of the 21st century. Is has been estimated that 350 million people suffer from this disease worldwide and unfortunately, this number is getting greater by the year. It has been forecasted that in the next years every third person will suffer from depression at some point of their life. Depression is characterized by mood and emotional disturbances. Untreated or inadequately treated, leads to death, most often by suicide. At present, it is known that depression, classified as an affective disease, has a very complex clinical picture, course and pathogenesis.

Among hypotheses attempting to explain the basis of depression, an increasing number of reports supports the immune theory of depression which highlights the significance of the immune system in etiology of this disease. It has been indicated that disturbances in the network of mediators of this system, i.e. cytokines and aggravation of peripheral inflammatory processes but most of all in the central nervous system, may be crucial for development of this disease.

Proinflammatory cytokines (IL-1β, IL-18) are mostly produced by immunocompetent cells, represented in the brain by microglia. They are small phagocytic cells, whose controlled activation is a beneficial process, necessary for maintaining homeostasis in the brain. However, their overactivation or prolonged activation in response to disadvantageous factors leads to exaggerated uncontrolled inflammatory reaction manifested by an increased release of proinflammatory cytokines in the brain, excessive activation of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production.

Recently, inflammasomes have attracted a considerable interest because they can play a role of sensors of many factors disturbing brain homeostasis, and among them the inflammasome NLRP3 (NLR family, pyrin domain containing 3) belongs to the best described. These protein complexes, composed of an intracellular receptor NLR, protein ASC and procaspase-1 precursor are a molecular platform in which inactive forms of proinflammatory cytokines: interleukin -1β and interleukin-18 are activated. With an active participation of the inflammasome, these cytokines are released from the cell to extracellular space and regulate the immune response in the brain.

Inflammatory processes are activated by different factors, including environmental conditions, of which the most common in the present world is stress. Up till now, many papers have demonstrated that stress increases the number of activated microglia cells, elevating synthesis of proinflammatory cytokines and other neurotoxic factors which leads to neuronal damage and consequently to emotional and cognitive disturbances [Kim et al., 2000; Gosheen et al., 2008, Ślusarczyk et al., 2015]. However, it has not been studied whether changes in the subunits of inflammasomes present in microglia cells can be relevant to behavioral deficits and to the mechanisms of action of antidepressant drugs used to treat them.

For this reason, **the aim of the present project is to determine whether the enhanced inflammatory activation in primary microglia cultures derived from animals subjected to a model of depression is connected with disturbances of the amount and function of NLRP3 complexes. The studies will be conducted in vivo in 3 months old males, offspring of control and stressed dams before and after chronic, 14-day administration of antidepressant drugs with different mechanism of action. Simultaneously, the studies will be conducted in vitro on primary glial cultures derived from the cerebral cortex of 2-day-old Sprague-Dawley rats from the control group and from an animal model of depression both under basal conditions and after an additional activation by the bacterial endotoxin (lipopolysaccharide, LPS).**

Biological studies of bases of diseases are often conducted in animals models. In the present project, we will use a commonly accepted and thoroughly described in literature animals model of depression based on the procedure of prenatal stress [Morley-Fletcher et al., 2003]. Its usefulness was confirmed by our earlier studies which demonstrated that 3 months old rats born to dams exposed to repeated stress in the third trimester of pregnancy exhibited an array of behavioral disturbances, changes in the hypothalamic-pituitary-adrenal (HPA) axis activity and immune system parameters [Szczesny et al., 2014], thus mimicking picture of this disease in humans. Antidepressant drugs used in clinical practice administered to animals in the above model normalized the observed deficits, which confirmed their therapeutic efficacy in the animal model of depression.

The planned studies will contribute to a better understanding of not only mechanisms underlying depression but also will broaden our knowledge of molecular mechanisms of action of antidepressant drugs. In the future, they may also be of practical significance in the choice of appropriate pharmacotherapy in patients, especially those suffering from treatment-resistant depression, which was suggested to be associated with exaggerated inflammatory activation, including IL-1β expression in the brain [Maes, 2001].

LITERATURE REFERENCES:

1. Gosheen I., Kreisel T., Ben-Menachem-Zidon O., Licht T., Weidenfeld J., Ben-Hur T., Yirmiya R. Brain interleukin-1 mediates chronić stress induced depression in mice via adrenocortical activation and hippocampal neurogenesis supression. Mol Psychiatry. 2008, 13:717-728.
2. Kim W.G., Mohney R.P., Wilson B., Jeohn G.H., Liu B., Hong J.S. Regional differences in susceptibility in lipopolisaccharide-induced neurotoxity in the rat brain: role of microglia. J Neurosci. 2000, 20(16): 6309-6316.
3. Maes M. Interleukin-1beta and the etiology of depression. Acta Psychiatr Scand. 2001 Mar;103(3):161-2.
4. Morley-Fletcher S., Darnaudery M.., Koehl M.., Casolini P., Van Reeth O., Maccari S.: Prenatal stress in rats predicts immobility behavior in the forced swim test. Effects of a chronic treatment with tianeptine. Brain Res. 2003, 989(2):246-251.
5. Ślusarczyk J., Trojan E., Glombik K., Budziszewska B., Kubera M., Lason M., Popiołek - Barczyk K., Mika J., Wedzony K., Basta-Kaim A. Prenatal stress is a vulnerability factor for altered morphology and biological activity of microglia cells. Front Cell Neurosci. 2015, 12;9:82

6. Szczesny E, Basta-Kaim A, Slusarczyk J, Trojan E, Glombik K, Regulska M, Leskiewicz M, Budziszewska B, Kubera M, Lason W.The impact of prenatal stress on insulin-like growth factor-1 and pro-inflammatory cytokine expression in the brains of adult male rats: the possible role of suppressors of cytokine signaling proteins. J Neuroimmunol. 2014 Nov 15;276(1-2):37-46.