Summary

Until now, studies in animal models of depression have been conducted primarily in males, while depression in our cultural area seems to be more common among women than men. Moreover, in research using lipopolysaccharide (LPS) to induce depressive-like behavior, LPS was injected usually once and caused short-term changes in behavior, while depression is a chronic disease. Therefore, one of the aims of research constituting the basis of my doctoral thesis was to develop a new model of depression in mice, based on repeated, intermittent LPS injections to males and females, to induce a long-lasting depression-like state.

Previously published studies, evaluating the influence of antidepressants on immunity, primarily concentrated on their impact on serum level of cytokines. There is a lack of evidence evaluating simultaneously the level of cytokines in the spleen and the central nervous system and analyzing connections between treatment-resistant depression and cytokines, antioxidant system or kynurenine pathway. There are also only a few studies investigating the effectiveness of antidepressants in elderly patients. Insufficient and inconclusive results suggested the need for further research. Therefore, the consecutive aim of this thesis was to delineate the impact of chronic mild stress (CMS), which is a well-validated model of depression, and prolonged administration of imipramine (IMI) on the kynurenine pathway (in some brain structures), markers of oxidative stress and antioxidant system (in the liver) in rats. Furthermore, the level of cytokines in some brain structures, parameters of peripheral cell-mediated immunity and impact of drugs on this immunity were assessed. The studies were conducted in three models of depression.

In the first part of my experiments, C57BL/6J mice received LPS intraperitoneally (i.p.) once daily for 5 consecutive days a month for 4 months. The LPS dose was increased every day in the first three days and was then gradually decreased on day 4 and 5 (day 1: 750 µg/kg b.w., day 2: 1000 µg/kg b.w., day 3: 1250 µg/kg b.w., day 4: 1000 µg/kg b.w., day 5: 750 µg/kg b.w.). Fluoxetine (FLU) administration started 28 days after the last dose of LPS. The sucrose consumption was measured throughout the experiment. LPS administrations caused a decrease in sucrose consumption lasting for at least 7
weeks. This effect was abolished by FLU administration. Repeated and intermittent LPS injections to mice can be a new useful model of depression. In addition, neuroimmunendocrine parameters were measured. The findings suggest that therapeutic efficacy of the drug can be connected with increasing the IL-10 production and lowering the superoxide and corticosterone production.

In the second part of the experiments, old female C57BL/6J mice (22-23 months old) were treated with FLU (10 mg/kg b.w., i.p.) for 11 days. After 7 days of drug administration, mice were injected both FLU and LPS (100 µg/kg b.w., i.p.) for 4 subsequent days. Drinking of 1% sucrose solutions was measured throughout the experiment. The forced swim-test was performed after the 10th FLU injection and third LPS dose. The results allowed for the conclusion that FLU did not reduce depressive behavior induced by LPS injection. However, the studies have proven anti-inflammatory effect of FLU evidenced by reduction of proinflammatory cytokine production in the spleen and hippocampus and enhancement of IL-10 production in the spleen.

The third and fourth parts of the experiments were performed on Wistar rats subjected to chronic mild stress model of depression. Administration of IMI (10 mg/kg b.w., i.p.) for 5 weeks to rats subjected to CMS resulted in significant reduction of anhedonia, measured by sucrose intake, in 80% of animals (CMS IMI-R). About 20% of rats did not respond to the IMI treatment (CMS IMI-NR).

The third part of experiments was performed on hepatocytes. In CMS IMI-NR rats, the level of malondialdehyde (MDA) was increased, whereas the levels of sulfane sulfur (SS) and non-protein sulfhydryl groups (NPSH) were decreased in comparison to CMS group. Moreover, in CMS IMI-NR rats the activity of antioxidant enzymes (glutathione peroxidase (GPx) and catalase (CAT)) was decreased compared to IMI-treated rats.

The fourth part of the research within the framework of my doctoral thesis concerning the kynurenine pathway, revealed that the lack of response to therapeutic action of IMI (CMS IMI-NR) could be connected with deficiency of the inhibitory properties of IMI on indoleamine 2,3-dioxygenase (IDO) and kynurenine 3-monoxygenase (KMO) mRNA expression in the cortex and IDO, KMO and kynurenine (KYN) synthesis in the cortex. Probably, increased level of interleukin (IL)-6 mRNA expression in the cortex and hippocampus also impacted on resistance to IMI.
The findings of the first part suggest a potential usefulness of the new model in future studies of depression. The results in the second part of the thesis, despite that they did not demonstrate antidepressant properties of FLU in senescent females, have proven profound anti-inflammatory properties of FLU. This property seems to be very important in elderly patients suffering from comorbidity of depression and inflammatory diseases. Although the results presented in the third part did not show a direct connection between oxidative stress in the liver and anhedonia, they revealed, that pro-oxidant action of IMI was particularly evident in IMI non-responding rats. This observation is crucial for patients resistant to this drug. In these people, IMI therapy should be discontinued immediately due to hepatotoxicity. Research described in the last part of my thesis allowed for evaluation of expression of enzymes and level of metabolites of the kynurenine pathway, also in animals non-responding to antidepressant treatment; this issue has not been explored by researchers, yet.